Clinical trial results:
A randomised, double-blind, placebo-controlled and parallel group trial to evaluate efficacy and safety of twice daily inhaled doses of BI 1265162 delivered by Respimat® inhaler as add-on therapy to standard of care over 4 weeks in patients with cystic fibrosis – BALANCE – CFTM 1

Summary

EudraCT number	2019-000261-21
Trial protocol	SE DE FR BE IE GB ES
Global end of trial date	24 April 2020

Results information

Result version number	v2 (current)
This version publication date	27 May 2021
First version publication date	01 May 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1399-0003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04059094
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim Call Center, Boehringer Ingelheim, +1 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim Call Center, Boehringer Ingelheim, +1 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	18 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2020
Global end of trial reached?	Yes
Global end of trial date	24 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to assess the efficacy, safety, and pharmacokinetics of different dose regimens of BI 1265162 versus placebo in adult and adolescent patients with cystic fibrosis. This trial examined twice daily inhaled doses of 20 microgram, 50 microgram, 100 microgram, and 200 microgram of BI 1265162 delivered by the Respimat® inhaler as an add-on to standard-of-care treatment for cystic fibrosis.

Protection of trial subjects:

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	74
EEA total number of subjects	54

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)	73
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial aimed to assess the efficacy, safety, and pharmacokinetics of different dose regimens of BI 1265162 taken twice daily by the Respimat® inhaler versus placebo in adult and adolescent patients with cystic fibrosis for a 4-week treatment period. Study was terminated without recruiting any adolescent patients.

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	Investigator, Monitor, Data analyst, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

2 puffs of matching placebo were inhaled orally via the Respimat® inhaler twice daily for a treatment period of 4 weeks in patients with cystic fibrosis.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

2 puffs of matching placebo were inhaled orally via the Respimat® inhaler twice daily for a treatment period of 4 weeks in patients with cystic fibrosis.

Arm title	BI 1265162 20µg b.i.d.

Arm description:

2 puffs of 10 micrograms (µg) BI 1265162 (Total: 20µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 40µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Arm type	Experimental
Investigational medicinal product name	BI 1265162 20µg b.i.d.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

2 puffs of 10 micrograms (µg) BI 1265162 (Total: 20µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 40µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Arm title	BI 1265162 50µg b.i.d.

Arm description:

2 puffs of 25 micrograms (µg) BI 1265162 (Total: 50µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 100µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Arm type	Experimental
Investigational medicinal product name	BI 1265162 50µg b.i.d.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

2 puffs of 25 micrograms (µg) BI 1265162 (Total: 50µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 100µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Arm title	BI 1265162 100µg b.i.d.

Arm description:

2 puffs of 50 micrograms (µg) BI 1265162 (Total: 100µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 200µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Arm type	Experimental
Investigational medicinal product name	BI 1265162 100µg b.i.d.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

2 puffs of 50 micrograms (µg) BI 1265162 (Total: 100µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 200µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Arm title	BI 1265162 200µg b.i.d.

Arm description:

2 puffs of 100 micrograms (µg) BI 1265162 (Total: 200µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 400µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Arm type	Experimental
Investigational medicinal product name	BI 1265162 200µg b.i.d.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

2 puffs of 100 micrograms (µg) BI 1265162 (Total: 200µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 400µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Number of subjects in period 1[1]	Placebo	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.
Started	18	6	5
Completed	18	4	5
Not completed	0	2	0
Not willing to travel due to COVID-19 pandemic	-	2	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 1[1]	BI 1265162 100µg b.i.d.	BI 1265162 200µg b.i.d.
Started	5	18

Completed	5	17
Not completed	0	1
Not willing to travel due to COVID-19 pandemic	-	-
Adverse event, non-fatal	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
2 puffs of matching placebo were inhaled orally via the Respimat® inhaler twice daily for a treatment period of 4 weeks in patients with cystic fibrosis.	
Reporting group title	BI 1265162 20µg b.i.d.
Reporting group description:	
2 puffs of 10 micrograms (µg) BI 1265162 (Total: 20µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 40µg) for a treatment period of 4 weeks in patients with cystic fibrosis.	
Reporting group title	BI 1265162 50µg b.i.d.
Reporting group description:	
2 puffs of 25 micrograms (µg) BI 1265162 (Total: 50µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 100µg) for a treatment period of 4 weeks in patients with cystic fibrosis.	
Reporting group title	BI 1265162 100µg b.i.d.
Reporting group description:	
2 puffs of 50 micrograms (µg) BI 1265162 (Total: 100µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 200µg) for a treatment period of 4 weeks in patients with cystic fibrosis.	
Reporting group title	BI 1265162 200µg b.i.d.
Reporting group description:	
2 puffs of 100 micrograms (µg) BI 1265162 (Total: 200µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 400µg) for a treatment period of 4 weeks in patients with cystic fibrosis.	

Reporting group values	Placebo	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.
Number of subjects	18	6	5
Age categorical			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
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)	18	6	5
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: years			
arithmetic mean	29.3	26.8	31.2
standard deviation	± 10.1	± 5.8	± 8.6

Sex: Female, Male			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: Participants			
Female	2	1	3
Male	16	5	2
Race (NIH/OMB)			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	17	6	5
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	17	6	5
Unknown or Not Reported	0	0	0
Trough forced expiratory volume in one second (FEV1) percent predicted			
Baseline trough FEV1 percent (%) predicted was defined as the last measurement taken on day 1 before first study drug administration and was measured within 30 minutes prior to dosing. Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received. One participant in the BI 1265162 200 microgram group did not have valid baseline trough FEV1 percent predicted value measured.			
Units: Percentage of predicted trough FEV1			
arithmetic mean	59.40	69.93	63.02
standard deviation	± 11.29	± 15.99	± 14.40

Reporting group values	BI 1265162 100µg b.i.d.	BI 1265162 200µg b.i.d.	Total
Number of subjects	5	18	52
Age categorical			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
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)	5	18	52

From 65-84 years	0	0	0
85 years and over	0	0	0

Age Continuous			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: years			
arithmetic mean	36.8	33.4	
standard deviation	± 4.2	± 10.2	-
Sex: Female, Male			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: Participants			
Female	1	3	10
Male	4	15	42
Race (NIH/OMB)			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	4	18	50
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	5	18	51
Unknown or Not Reported	0	0	0
Trough forced expiratory volume in one second (FEV1) percent predicted			
Baseline trough FEV1 percent (%) predicted was defined as the last measurement taken on day 1 before first study drug administration and was measured within 30 minutes prior to dosing. Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received. One participant in the BI 1265162 200 microgram group did not have valid baseline trough FEV1 percent predicted value measured.			
Units: Percentage of predicted trough FEV1			
arithmetic mean	65.50	57.94	
standard deviation	± 7.00	± 13.76	-

Subject analysis sets

Subject analysis set title	Total with baseline FEV1 measures
Subject analysis set type	Full analysis

Subject analysis set description:

Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received. One participant in the BI 1265162 200 microgram group did not have valid baseline trough forced expiratory volume in one second (FEV1) percent predicted value measured.

Reporting group values	Total with baseline FEV1 measures		
Number of subjects	51		
Age categorical			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: years arithmetic mean standard deviation	±		
Sex: Female, Male			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: Participants			
Female Male			
Race (NIH/OMB)			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			
Ethnicity (NIH/OMB)			
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.			
Units: Subjects			

Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			

Trough forced expiratory volume in one second (FEV1) percent predicted			
Baseline trough FEV1 percent (%) predicted was defined as the last measurement taken on day 1 before first study drug administration and was measured within 30 minutes prior to dosing. Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received. One participant in the BI 1265162 200 microgram group did not have valid baseline trough FEV1 percent predicted value measured.			
Units: Percentage of predicted trough FEV1 arithmetic mean standard deviation	 61.11 ± 12.89		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
2 puffs of matching placebo were inhaled orally via the Respimat® inhaler twice daily for a treatment period of 4 weeks in patients with cystic fibrosis.	
Reporting group title	BI 1265162 20µg b.i.d.
Reporting group description:	
2 puffs of 10 micrograms (µg) BI 1265162 (Total: 20µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 40µg) for a treatment period of 4 weeks in patients with cystic fibrosis.	
Reporting group title	BI 1265162 50µg b.i.d.
Reporting group description:	
2 puffs of 25 micrograms (µg) BI 1265162 (Total: 50µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 100µg) for a treatment period of 4 weeks in patients with cystic fibrosis.	
Reporting group title	BI 1265162 100µg b.i.d.
Reporting group description:	
2 puffs of 50 micrograms (µg) BI 1265162 (Total: 100µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 200µg) for a treatment period of 4 weeks in patients with cystic fibrosis.	
Reporting group title	BI 1265162 200µg b.i.d.
Reporting group description:	
2 puffs of 100 micrograms (µg) BI 1265162 (Total: 200µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily dose: 400µg) for a treatment period of 4 weeks in patients with cystic fibrosis.	
Subject analysis set title	Total with baseline FEV1 measures
Subject analysis set type	Full analysis
Subject analysis set description:	
Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received. One participant in the BI 1265162 200 microgram group did not have valid baseline trough forced expiratory volume in one second (FEV1) percent predicted value measured.	

Primary: Change from baseline in percent predicted trough Forced Expiratory Volume in 1 Second (FEV1) after 4 weeks of treatment

End point title	Change from baseline in percent predicted trough Forced Expiratory Volume in 1 Second (FEV1) after 4 weeks of treatment
End point description:	
Trough FEV1 was measured within 30 minutes prior to dosing of study medication. Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received. Only participants with non-missing outcome measured were included in the analysis.	
End point type	Primary
End point timeframe:	
At 30 minutes prior to dosing in Day 1 (baseline) and Day 29 (end of 4-week treatment period).	

End point values	Placebo	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.	BI 1265162 100µg b.i.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	4	5	5
Units: Percentage of predicted trough FEV1				
arithmetic mean (standard deviation)	-0.6 (± 8.03)	-0.5 (± 2.82)	-0.22 (± 2.62)	2.82 (± 3.57)

End point values	BI 1265162 200µg b.i.d.			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Percentage of predicted trough FEV1				
arithmetic mean (standard deviation)	0.45 (± 5.42)			

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM) with fixed effects for baseline, visit, treatment, treatment-by-visit interaction, baseline-by-visit interaction, and random effect for patient was applied. No hypothesis testing was performed, as this trial was prematurely discontinued. MMRM only included data from 200µg BI and placebo, as the sample size of the BI 20µg, BI 50µg and BI 100µg dose levels was limited because of the premature discontinuation of the trial.

Comparison groups	Placebo v BI 1265162 200µg b.i.d.
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5468
Method	Mixed model with repeated measurements
Parameter estimate	Adjusted means difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	6.5
Variability estimate	Standard error of the mean
Dispersion value	2.45

Secondary: Change from baseline in Lung Clearance Index (LCI) assessed by N2 Multiple Breath Washout (N2MBW) procedure after 4 weeks of treatment

End point title	Change from baseline in Lung Clearance Index (LCI) assessed by N2 Multiple Breath Washout (N2MBW) procedure after 4 weeks of treatment

End point description:

Change from baseline in Lung Clearance Index (LCI) assessed by N2 Multiple Breath Washout (N2MBW) procedure after 4 weeks of treatment was reported. LCI was calculated as the ratio of cumulative expired volume (CEV) to functional residual capacity (FRC), which was LCI = CEV (milliliter/kilogram) / FRC (milliliter/kilogram) and hence, LCI was "Unitless". The change from baseline after 4 weeks of treatment in LCI was then calculated as the LCI value measured after 4 weeks of treatment at Day 29 minus the LCI value measured at baseline on Day 1. Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received. Only participants with non-missing outcome measured were included in the analysis. '99999' stands for 'not available' since data from only one patient was available and no standard deviation could be calculated.

End point type	Secondary

End point timeframe:

At pre-dose in Day 1 (baseline) and Day 29 (end of 4-week treatment period).

End point values	Placebo	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.	BI 1265162 100µg b.i.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	0[1]	1[2]	1[3]
Units: Unitless				
arithmetic mean (standard deviation)	-0.824 (± 3.312)	()	-0.238 (± 99999)	-2.547 (± 99999)

Notes:

[1] - No outcome data were collected for this group.

[2] - '99999' stands for 'not available'.

[3] - '99999' stands for 'not available'.

End point values	BI 1265162 200µg b.i.d.			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Unitless				
arithmetic mean (standard deviation)	-0.081 (± 1.001)			

Statistical analyses

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

ANCOVA based on analysis of covariance with fixed effects for baseline and treatment was applied. Statistical analysis was performed for 200µg BI and placebo groups only. No hypothesis testing was performed, as this trial was prematurely discontinued. ANCOVA only included data from 200µg BI and placebo, as the sample size of the BI 20µg, BI 50µg and BI 100µg dose levels was limited because of the premature discontinuation of the trial.

Comparison groups	Placebo v BI 1265162 200µg b.i.d.
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3039
Method	ANCOVA
Parameter estimate	Adjuste means difference
Point estimate	2.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	6.5
Variability estimate	Standard error of the mean
Dispersion value	1.83

Secondary: Change from baseline in Cystic Fibrosis Questionnaire Revised (CFQ-R) total score after 4 weeks of treatment

End point title	Change from baseline in Cystic Fibrosis Questionnaire Revised (CFQ-R) total score after 4 weeks of treatment

End point description:

The adult/adolescent format of the CFQ-R consists of 50 questions (qts) dividing into 12 domains: Physical functioning(8 qts), role limitations(4 qts), vitality(4 qts), emotional functioning(5 qts), social functioning(6 qts), body image(3 qts), eating disturbance(3 qts), treatment burden(3 qts), health perceptions(3 qts), weight(1 qts), respiratory symptoms(7 qts), and digestive system(3 qts). The score of some qts is first reversed if reversed coded, so that the score for each of the 50 qts ranges from 1 to 4 points (less symptoms). Then, a domain score for a domain with N qts is calculated as (sum of the scores of the N qts - N)/(N 4 – N) 100. Each domain score ranges from 0 to 100 (better health). The CFQ-R total score is summing up the domain scores and ranges from 0 to 1200 (better quality of life). Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. Only patients with non-missing outcomes were included.

End point type	Secondary

End point timeframe:

At Day 1 (baseline) and Day 29 (end of 4-week treatment period).

End point values	Placebo	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.	BI 1265162 100µg b.i.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	6	5	5
Units: Score on a scale				
arithmetic mean (standard deviation)	5.941 (± 76.669)	27.083 (± 61.626)	11.167 (± 33.968)	-15.611 (± 62.167)

End point values	BI 1265162 200µg b.i.d.			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Score on a scale				
arithmetic mean (standard deviation)	24.236 (± 58.290)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q) (4 separate sub-scores) after 4 weeks of treatment

End point title	Change from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q) (4 separate sub-scores) after 4 weeks of treatment

End point description:

The 20-item Sputum Assessment Questionnaire (CASA-Q) consisted of 4 domains: Cough Symptoms Domain (3 items), Cough Impact Domain (8 items), Sputum Symptoms Domain (3 items), and Sputum Impact Domain (6 items). Score of each item has been reversed such that better responses have higher score, which ranges from 1 (worse) to 5 (better health). For each domain, the domain score was calculated by summing up the scores of the respective items and scaling to a score ranging from 0 to 100, with higher score associated with fewer symptoms/less impact due to cough or sputum. Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received. Only participants with non-missing outcome measured were included in the analysis.

End point type	Secondary

End point timeframe:

At Day 1 (baseline) and Day 29 (end of 4-week treatment period).

End point values	Placebo	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.	BI 1265162 100µg b.i.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	4	5	5
Units: Score on a scale				
arithmetic mean (standard deviation)				
Cough Symptom Domain Score	4.167 (± 18.798)	10.417 (± 17.180)	8.333 (± 8.333)	3.333 (± 24.008)
Cough Impact Domain Score	-0.521 (± 16.648)	-6.250 (± 12.758)	-0.625 (± 12.771)	1.250 (± 14.757)
Sputum Symptom Domain Score	5.093 (± 15.950)	4.167 (± 8.333)	10.000 (± 14.907)	3.333 (± 16.245)
Sputum Impact Domain Score	-0.694 (± 16.497)	-4.167 (± 3.402)	5.000 (± 11.562)	-0.833 (± 13.944)

End point values	BI 1265162 200µg b.i.d.			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Cough Symptom Domain Score	5.392 (± 15.574)			
Cough Impact Domain Score	0.735 (± 11.187)			
Sputum Symptom Domain Score	5.392 (± 19.530)			
Sputum Impact Domain Score	0.490 (± 11.110)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with treatment-emergent Adverse Events (AE) up to day 36

End point title	Percentage of patients with treatment-emergent Adverse Events (AE) up to day 36

End point description:

Percentage of patients with any treatment-emergent Adverse Events (AE) up to day 36 was reported. Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.

End point type	Secondary

End point timeframe:

From Day 1 (baseline) until end of 4 weeks of treatment period (Day 29) plus 7 days of follow-up, up to 36 days.

End point values	Placebo	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.	BI 1265162 100µg b.i.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	6	5	5
Units: Percentage of participants				
number (not applicable)	66.7	0	40.0	40.0

End point values	BI 1265162 200µg b.i.d.			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (not applicable)	83.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of BI 1265162 in plasma at 0.083 hour at steady state following dose 15 (C0.083,ss,15)

End point title	Concentration of BI 1265162 in plasma at 0.083 hour at steady state following dose 15 (C0.083,ss,15)[4]

End point description:

Concentration of BI 1265162 in plasma at 0.083 hour at steady state following dose 15 (C0.083,ss,15) was reported. Pharmacokinetic set (PKS): The PKS included all patients in the treated set who provided at least one pharmacokinetic parameter. Only participants with non-missing outcome measured were included in the analysis.

End point type	Secondary

End point timeframe:

At 5 minutes (around 0.083 hours) post dosing at steady state on Day 8 for dose 15 (morning dose on Day 8).

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.	BI 1265162 100µg b.i.d.	BI 1265162 200µg b.i.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	4	16
Units: picomole/liter (pmol/L)				
geometric mean (geometric coefficient of variation)	207 (± 59.9)	471 (± 30.0)	1010 (± 20.1)	1110 (± 84.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of BI 1265162 in plasma at 0.083 hour at steady state following dose 57 (C0.083,ss,57)

End point title	Concentration of BI 1265162 in plasma at 0.083 hour at steady state following dose 57 (C0.083,ss,57)[5]

End point description:

Concentration of BI 1265162 in plasma at 0.083 hour at steady state following dose 57 (C0.083,ss,57) was reported. Pharmacokinetic set (PKS): The PKS included all patients in the treated set who provided at least one pharmacokinetic parameter. Only participants with non-missing outcome measured were included in the analysis.

End point type	Secondary

End point timeframe:

At 5 minutes (around 0.083 hours) post dosing at steady state on Day 29 for dose 57 (morning dose on Day 29).

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.	BI 1265162 100µg b.i.d.	BI 1265162 200µg b.i.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	5	14
Units: picomole/liter (pmol/L)				
geometric mean (geometric coefficient of variation)	162 (± 76.3)	463 (± 15.4)	573 (± 94.0)	1080 (± 165)

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose concentration measured of BI 1265162 in plasma at steady state after dose 15 (Cpre,ss, 15)

End point title	Pre-dose concentration measured of BI 1265162 in plasma at steady state after dose 15 (Cpre,ss, 15)[6]

End point description:

Pre-dose concentration measured of BI 1265162 in plasma at steady state after dose 15 (Cpre,ss, 15) was reported. Pharmacokinetic set (PKS): The PKS included all patients in the treated set who provided at least one pharmacokinetic parameter. Only participants with non-missing outcome measured were included in the analysis.

End point type	Secondary

End point timeframe:

At pre-dose (taken within 60 minutes prior to dosing) at steady state on Day 8 for dose 15 (morning dose on Day 8).

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.	BI 1265162 100µg b.i.d.	BI 1265162 200µg b.i.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	5	14
Units: picomole/liter (pmol/L)				
geometric mean (geometric coefficient of variation)	7.82 (± 28.0)	24.3 (± 31.8)	38.4 (± 292)	43.8 (± 95.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose concentration measured of BI 1265162 in plasma at steady state after dose 57 (Cpre,ss, 57)

End point title	Pre-dose concentration measured of BI 1265162 in plasma at steady state after dose 57 (Cpre,ss, 57)[7]

End point description:

Pre-dose concentration measured of BI 1265162 in plasma at steady state after dose 57 (Cpre,ss, 57) was reported. Pharmacokinetic set (PKS): The PKS included all patients in the treated set who provided at least one pharmacokinetic parameter. Only participants with non-missing outcome measured were included in the analysis. '99999' stands for 'not available' since no descriptive statistics calculated since not enough data as only 1 patient was analyzed.

End point type	Secondary

End point timeframe:

At pre-dose (taken within 60 minutes prior to dosing) at steady state on Day 29 for dose 57 (morning dose on Day 29).

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.	BI 1265162 100µg b.i.d.	BI 1265162 200µg b.i.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[8]	3	3	12
Units: picomole/liter (pmol/L)				
geometric mean (geometric coefficient of variation)	99999 (± 99999)	13.0 (± 80.8)	22.3 (± 48.3)	37.2 (± 56.9)

Notes:

[8] - '99999' stands for 'not available'.

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve of BI 1265162 in plasma from 0 to 4 hours at steady state after dose 15 (AUC0-4,ss,15)

End point title	Area under the concentration-time curve of BI 1265162 in plasma from 0 to 4 hours at steady state after dose 15 (AUC0-4,ss,15)[9]

End point description:

Area under the concentration-time curve of BI 1265162 in plasma from 0 to 4 hours at steady state after dose 15 (AUC0-4,ss,15) was reported. Pharmacokinetic set (PKS): The PKS included all patients in the treated set who provided at least one pharmacokinetic parameter. Only participants with non-missing outcome measured were included in the analysis.

End point type	Secondary

End point timeframe:

At pre-dose (taken within 60 minutes prior to dosing) and 5 minutes (min), 30 min, 1 hour, and 4 hours post dosing at steady state on Day 8 for dose 15 (morning dose on Day 8).

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.	BI 1265162 100µg b.i.d.	BI 1265162 200µg b.i.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	4	4	17
Units: hours * picomole/liter (h*pmol/L)				
geometric mean (geometric coefficient of variation)	192 (± 45.3)	541 (± 19.1)	1020 (± 8.93)	1380 (± 71.0)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 (baseline) until end of 4 weeks of treatment period (Day 29) plus 7 days of follow-up, up to 36 days.

Adverse event reporting additional description:

Treated set (TS): The TS included all patients who were randomized and treated with at least one dose of study drug. The treatment assignment was determined based on the first treatment the subjects received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

2 puffs of matching placebo were inhaled orally via the Respimat® inhaler twice daily for a treatment period of 4 weeks in patients with cystic fibrosis.

Reporting group title	BI 1265162 20µg b.i.d.

Reporting group description:

2 puffs of 10 micrograms (µg) BI 1265162 (Total: 20µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily
dose: 40µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Reporting group title	BI 1265162 50µg b.i.d.

Reporting group description:

2 puffs of 25 micrograms (µg) BI 1265162 (Total: 50µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily
dose: 100µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Reporting group title	BI 1265162 100µg b.i.d.

Reporting group description:

2 puffs of 50 micrograms (µg) BI 1265162 (Total: 100µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily
dose: 200µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Reporting group title	BI 1265162 200µg b.i.d.

Reporting group description:

2 puffs of 100 micrograms (µg) BI 1265162 (Total: 200µg) were inhaled orally via the Respimat® inhaler twice daily (b.i.d., daily
dose: 400µg) for a treatment period of 4 weeks in patients with cystic fibrosis.

Serious adverse events	Placebo	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Respiratory, thoracic and mediastinal disorders			
Pulmonary congestion			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (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
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Serious adverse events	BI 1265162 100µg b.i.d.	BI 1265162 200µg b.i.d.	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary congestion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	BI 1265162 20µg b.i.d.	BI 1265162 50µg b.i.d.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 18 (61.11%)	0 / 6 (0.00%)	2 / 5 (40.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pulmonary function test decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Hypoaesthesia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site haematoma			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

Lacrimation increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Bronchial obstruction			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract congestion			

subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasal polyps			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Sputum increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	4 / 18 (22.22%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	4	0	0
Pneumonia bacterial			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	BI 1265162 100µg b.i.d.	BI 1265162 200µg b.i.d.	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	15 / 18 (83.33%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pulmonary function test decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 5 (20.00%)	2 / 18 (11.11%)	
occurrences (all)	2	2	
Hypoaesthesia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Vessel puncture site haematoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	
occurrences (all)	0	0	
Bronchial obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	1 / 5 (20.00%)	3 / 18 (16.67%)	
occurrences (all)	1	3	
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	
occurrences (all)	0	0	
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Lower respiratory tract congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	
occurrences (all)	0	0	
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nasal polyps			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	
occurrences (all)	0	0	
Sputum increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 18 (0.00%)	
occurrences (all)	0	0	
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Pneumonia bacterial			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Rhinitis			

subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2019	introduced administrative changes, provided additional clarification, removed inconsistencies, introduced flexibility, and corrected errors in the original protocol. - Changed the secondary pharmacokinetic endpoint from Cmax,N to Ct,N; Ct,N was more in-line with the sparse sampling plan for pharmacokinetics - Adapted inclusion criterion 5 and exclusion criterion 15; these changes removed the requirement of the use of birth control for males able to father a child and simultaneously allowed the recruitment of women of child-bearing potential who used adequate contraception - Added pregnancy testing for the women of child-bearing potential who were allowed into the trial based on Global Amendment 1 - Added a description of procedures that would have to be followed in the event that a woman of child-bearing potential became pregnant during the trial, and - Added chloride, inorganic phosphorus, and calcium to the list of electrolytes to be analysed as part of safety laboratory tests - Required that each result of elevated serum potassium levels be confirmed by either a second measurement or by the presence of clinical symptoms.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This trial was prematurely discontinued with only adult patients being recruited based on the results of a pre-specified interim futility analysis that indicated insufficient efficacy.

Notes: