Clinical trial results:
A Phase IIa, two-part, randomised, multi-centre, multinational, double-blind, placebo-controlled, parallel group study to compare the efficacy and safety of BCT197 when added on to standard of care for the treatment of acute respiratory exacerbations of chronic obstructive pulmonary disease (COPD) requiring hospitalisation in adults.

Summary

EudraCT number	2015-004631-13
Trial protocol	LV HU GB RO CZ DE BG IT
Global end of trial date	07 November 2017

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	MBCT206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02700919
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mereo BioPharma 1 Ltd
Sponsor organisation address	4th Floor, 1 Cavendish Place, London, United Kingdom, W1G 0QF
Public contact	William Moore, Mereo BioPharma Group, +44 (0) 333 023 7300, enquiries@mereobiopharma.com
Scientific contact	Jackie Parkin, Mereo BioPharma Group, +44 (0) 333 023 7300, enquiries@mereobiopharma.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	07 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of two different dosing regimens of BCT197 added to standard of care (SoC) versus placebo added to SoC in the treatment of acute respiratory exacerbations of COPD that required hospitalisation by comparison of change in forced expiratory volume in 1 second (FEV1) from Baseline (pre-dose) to Day 7.

Protection of trial subjects:

This study was conducted in accordance with current applicable regulations, International Council for Harmonisation (ICH) guidelines, and local legal requirements. It complies with the ethical principles described in the 18th World Medical Assembly (Helsinki 1964) and amendments of the 29th (Tokyo 1975), 35th (Venice 1983), 41st (Hong Kong 1989), and 48th (South Africa 1996) World Medical Assemblies, Declaration of Helsinki.

The risk to subjects in this study were minimised by compliance with the inclusion/exclusion criteria, close clinical monitoring, including signs and symptoms related to the potential risks of p38 mitogen-activated protein kinase inhibitors for at least 25 weeks following the last dose of study medication. Additional stringent monitoring for inclusion in the study with specific observation for any class effects was performed throughout the study.

Background therapy:

This study did not restrict the appropriate care of the subject and allowed the use of the current institution SoC with respect to dose, regimens, duration of treatment for medical treatment of the subject. In agreement with the updated version of global initiative for chronic obstructive lung disease (2015) for the treatment of acute exacerbations of COPD, subjects must have been receiving at least steroids and/or antibiotics. However medications that may have interfered with metabolism of the study drug or that may have brought additional risk to the subject were to be avoided. Subjects were eligible only if their SoC treatment had been initiated less than 24 hours before randomisation and dosing.

Evidence for comparator: -

Actual start date of recruitment	01 August 2016
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	Poland: 27
Country: Number of subjects enrolled	Romania: 30
Country: Number of subjects enrolled	Bulgaria: 94
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 64
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Latvia: 10

Country: Number of subjects enrolled	Russian Federation: 37
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	279
EEA total number of subjects	241

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)	137
From 65 to 84 years	140
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at 52 investigator centres in 10 countries worldwide. The target population was subjects with acute severe exacerbations requiring hospitalisation; patients with this condition are usually expected to be treated in the emergency room (ER). Multiple inclusion criteria were used to enrich for the diagnosis of COPD.

Pre-assignment

Screening details:

Subjects were screened on the day they presented with an acute exacerbation (Day 1); there was no separate Screening Visit as subjects received their first dose of study treatment within 24 hours of presenting with an acute exacerbation. Of the 335 subjects screened for entry into the study, 282 were randomized and 279 received study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BCT197 High Dose Regimen

Arm description:

Participants received 75 mg BCT197 orally on Day 1. Subsequent doses with 40 mg BCT197 were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.

Arm type	Experimental
Investigational medicinal product name	BCT197
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

BCT197 hard gelatine capsules were administered orally with fluids at the same time of day at a dose of 75 mg (1 capsule of 50 mg and 1 capsule of 25 mg) on Day 1 and at a dose of 40 mg (2 capsules of 20 mg) on Day 3 and Day 5.

Arm title	BCT197 Low Dose Regimen

Arm description:

Participants received 40 mg BCT197 orally on Day 1. Subsequent doses with 20 mg BCT197 were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.

Arm type	Experimental
Investigational medicinal product name	BCT197
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

BCT197 hard gelatine capsules were administered orally with fluids at the same time of day at a dose of 40 mg (2 capsules of 20 mg) on Day 1 and at a dose of 20 mg (1 capsule of 20 mg) on Day 3 and Day 5.

Arm title	Placebo

Arm description:

Participants received placebo orally on Day 1. Subsequent doses with placebo were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.

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

Dosage and administration details:

Two matching placebo capsules were administered orally with fluids at the same time of day on Day 1, Day 3, and Day 5.

Number of subjects in period 1	BCT197 High Dose Regimen	BCT197 Low Dose Regimen	Placebo
Started	92	96	91
Completed	82	85	87
Not completed	10	11	4
Adverse event, serious fatal	1	-	-
Physician decision	1	-	-
Consent withdrawn by subject	5	8	2
Adverse event, non-fatal	-	3	1
Not specified	1	-	1
Lost to follow-up	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	BCT197 High Dose Regimen
Reporting group description:	
Participants received 75 mg BCT197 orally on Day 1. Subsequent doses with 40 mg BCT197 were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.	
Reporting group title	BCT197 Low Dose Regimen
Reporting group description:	
Participants received 40 mg BCT197 orally on Day 1. Subsequent doses with 20 mg BCT197 were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo orally on Day 1. Subsequent doses with placebo were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.	

Reporting group values	BCT197 High Dose Regimen	BCT197 Low Dose Regimen	Placebo
Number of subjects	92	96	91
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.8	63.3	64.9
standard deviation	± 8.21	± 8.68	± 7.34
Gender categorical Units: Subjects			
Female	24	28	30
Male	68	68	61
Race/Ethnicity Units: Subjects			
Asian	0	1	0
White	92	95	90
Other	0	0	1
FEV1 at Screening: Pre-bronchodilator			
Until Protocol V3.0 (Amendment 2), all spirometry measurements at Screening were conducted pre- and post-bronchodilator. From Protocol V4.0 (Amendment 3), spirometry at Screening was performed on-bronchodilator in the acute exacerbation setting. This was taken after any regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication.			
Units: litre(s)			
arithmetic mean	0.875	0.871	0.921
standard deviation	± 0.3649	± 0.3091	± 0.2775
FEV1 at Screening: Post-bronchodilator			
Until Protocol V3.0 (Amendment 2), all spirometry measurements at Screening were conducted pre- and post-bronchodilator. From Protocol V4.0 (Amendment 3), spirometry at Screening was performed on-bronchodilator in the acute exacerbation setting. This was taken after any regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication.			
Units: litre(s)			
arithmetic mean	1.149	1.040	1.029
standard deviation	± 0.4051	± 0.4030	± 0.3551

Forced Vital Capacity (FVC) at Screening: Pre-bronchodilator			
Until Protocol V3.0 (Amendment 2), all spirometry measurements at Screening were conducted pre- and post-bronchodilator. From Protocol V4.0 (Amendment 3), spirometry at Screening was performed on-bronchodilator in the acute exacerbation setting. This was taken after any regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication.			
Units: litre(s)			
arithmetic mean	2.410	2.137	2.352
standard deviation	± 0.8883	± 0.8675	± 0.7623
FVC at Screening – Post-bronchodilator			
Until Protocol V3.0 (Amendment 2), all spirometry measurements at Screening were conducted pre- and post-bronchodilator. From Protocol V4.0 (Amendment 3), spirometry at Screening was performed on-bronchodilator in the acute exacerbation setting. This was taken after any regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication.			
Units: litre(s)			
arithmetic mean	2.644	2.503	2.424
standard deviation	± 0.8443	± 0.8507	± 0.7262

Reporting group values	Total		
Number of subjects	279		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	82		
Male	197		
Race/Ethnicity			
Units: Subjects			
Asian	1		
White	277		
Other	1		
FEV1 at Screening: Pre-bronchodilator			
Until Protocol V3.0 (Amendment 2), all spirometry measurements at Screening were conducted pre- and post-bronchodilator. From Protocol V4.0 (Amendment 3), spirometry at Screening was performed on-bronchodilator in the acute exacerbation setting. This was taken after any regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication.			
Units: litre(s)			
arithmetic mean			
standard deviation	-		
FEV1 at Screening: Post-bronchodilator			
Until Protocol V3.0 (Amendment 2), all spirometry measurements at Screening were conducted pre- and post-bronchodilator. From Protocol V4.0 (Amendment 3), spirometry at Screening was performed on-bronchodilator in the acute exacerbation setting. This was taken after any regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication.			
Units: litre(s)			
arithmetic mean			
standard deviation	-		
Forced Vital Capacity (FVC) at Screening: Pre-bronchodilator			
Until Protocol V3.0 (Amendment 2), all spirometry measurements at Screening were conducted pre- and post-bronchodilator. From Protocol V4.0 (Amendment 3), spirometry at Screening was performed on-			

bronchodilator in the acute exacerbation setting. This was taken after any regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication.			
Units: litre(s) arithmetic mean standard deviation	- 		
FVC at Screening – Post-bronchodilator			
Until Protocol V3.0 (Amendment 2), all spirometry measurements at Screening were conducted pre- and post-bronchodilator. From Protocol V4.0 (Amendment 3), spirometry at Screening was performed on-bronchodilator in the acute exacerbation setting. This was taken after any regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication.			
Units: litre(s) arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	BCT197 High Dose Regimen
Reporting group description:	
Participants received 75 mg BCT197 orally on Day 1. Subsequent doses with 40 mg BCT197 were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.	
Reporting group title	BCT197 Low Dose Regimen
Reporting group description:	
Participants received 40 mg BCT197 orally on Day 1. Subsequent doses with 20 mg BCT197 were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo orally on Day 1. Subsequent doses with placebo were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.	
Subject analysis set title	BCT197 High Dose Regimen - ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Included all randomized subjects who received at least one high dose of BCT197 and who provided a Baseline and at least one post-Baseline FEV1 value.	
Subject analysis set title	BCT197 Low Dose Regimen - ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Included all randomized subjects who received at least one low dose of BCT197 and who provided a Baseline and at least one post-Baseline FEV1 value.	
Subject analysis set title	Placebo - ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Included all randomized subjects who received at least one dose of placebo study medication and who provided a Baseline and at least one post-Baseline FEV1 value.	
Subject analysis set title	BCT197 High Dose Regimen - PK Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetic (PK) Population - All participants who received at least one high dose BCT197 administration and had at least one quantifiable plasma concentration.	
Subject analysis set title	BCT197 Low Dose Regimen - PK Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants who received at least one low dose BCT197 administration and had at least one quantifiable plasma concentration.	

Primary: Change From Baseline in FEV1 to Day 7 - ITT Population

End point title	Change From Baseline in FEV1 to Day 7 - ITT Population
End point description:	
FEV1 data were recorded daily from Days 1 to 7 of the study using a computer-operated spirometer. Analysis was based on a linear Mixed Model for Repeated Measures (MMRM) with change from Baseline in parameter as outcome; including treatment, visit, treatment by visit interaction, severity of airflow limitation at Baseline, blood eosinophils (%) at Baseline, time from start of current COPD exacerbation to first study treatment dosing, presence of cardiovascular comorbidities at Screening and COPD exacerbation treatment at Screening as fixed effects, and Baseline value and Baseline by visit interaction as covariates. Baseline was defined as the last non-missing value collected before the first study treatment administration, including unscheduled assessments. Results were presented with adjusted mean difference (95% confidence interval [CI]).	
End point type	Primary

End point timeframe:

Days 1 to 7

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: litre(s)				
arithmetic mean (confidence interval 95%)	0.084 (0.019 to 0.149)	0.115 (0.049 to 0.180)	0.057 (-0.011 to 0.125)	

Statistical analyses

Statistical analysis title	Analysis of High Dose regimen

Statistical analysis description:

Linear mixed model for repeated measures (MMRMs) with change from Baseline in parameter as outcome; including treatment, visit, treatment by visit interaction, severity of airflow limitation at Baseline, blood eosinophils (%) at Baseline, time from start of current COPD exacerbation to first dosing, presence of cardiovascular comorbidities at Screening, and COPD exacerbation treatment at Screening as fixed effects, and Baseline value and Baseline by visit interaction as covariates.

Comparison groups	BCT197 High Dose Regimen - ITT Population v BCT197 Low Dose Regimen - ITT Population v Placebo - ITT Population
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Mixed models analysis

Statistical analysis title	Analysis of Low Dose regimen

Statistical analysis description:

Linear MMRMs with change from Baseline in parameter as outcome; including treatment, visit, treatment by visit interaction, severity of airflow limitation at Baseline, blood eosinophils (%) at Baseline, time from start of current COPD exacerbation to first dosing, presence of cardiovascular comorbidities at Screening, and COPD exacerbation treatment at Screening as fixed effects, and Baseline value and Baseline by visit interaction as covariates.

Comparison groups	BCT197 Low Dose Regimen - ITT Population v BCT197 High Dose Regimen - ITT Population v Placebo - ITT Population
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis

Statistical analysis title	Analysis of Placebo

Statistical analysis description:

Linear MMRMs with change from Baseline in parameter as outcome; including treatment, visit, treatment by visit interaction, severity of airflow limitation at Baseline, blood eosinophils (%) at Baseline, time from start of current COPD exacerbation to first IMP dosing, presence of cardiovascular comorbidities at Screening, and COPD exacerbation treatment at Screening as fixed effects, and Baseline value and Baseline by visit interaction as covariates.

Comparison groups	Placebo - ITT Population v BCT197 High Dose Regimen - ITT Population v BCT197 Low Dose Regimen - ITT Population
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.102
Method	Mixed models analysis

Statistical analysis title	Analysis of High Dose regimen vs Placebo

Statistical analysis description:

Linear MMRMs with change from Baseline in parameter as outcome; including treatment, visit, treatment by visit interaction, severity of airflow limitation at Baseline, blood eosinophils (%) at Baseline, time from start of current COPD exacerbation to first dosing, presence of cardiovascular comorbidities at Screening, and COPD exacerbation treatment at Screening as fixed effects, and Baseline value and Baseline by visit interaction as covariates.

Comparison groups	BCT197 High Dose Regimen - ITT Population v Placebo - ITT Population
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.507
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.053
upper limit	0.107

Statistical analysis title	Analysis of Low Dose Regimen vs Placebo

Statistical analysis description:

Linear MMRMs with change from Baseline in parameter as outcome; including treatment, visit, treatment by visit interaction, severity of airflow limitation at Baseline, blood eosinophils (%) at Baseline, time from start of current COPD exacerbation to first dosing, presence of cardiovascular comorbidities at Screening, and COPD exacerbation treatment at Screening as fixed effects, and Baseline value and Baseline by visit interaction as covariates.

Comparison groups	BCT197 Low Dose Regimen - ITT Population v Placebo - ITT Population

Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.148
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.136

Statistical analysis title	Analysis of High vs Low Dose Regimen

Statistical analysis description:

Linear MMRMs with change from Baseline in parameter as outcome; including treatment, visit, treatment by visit interaction, severity of airflow limitation at Baseline, blood eosinophils (%) at Baseline, time from start of current COPD exacerbation to first dosing, presence of cardiovascular comorbidities at Screening, and COPD exacerbation treatment at Screening as fixed effects, and Baseline value and Baseline by visit interaction as covariates.

Comparison groups	BCT197 High Dose Regimen - ITT Population v BCT197 Low Dose Regimen - ITT Population
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.443
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.109
upper limit	0.048

Secondary: Change From Baseline in FEV1 on Days 3, 10, and 14 - ITT Population

End point title	Change From Baseline in FEV1 on Days 3, 10, and 14 - ITT Population

End point description:

FEV1 data were recorded daily from Days 1 to 7, and Days 10 and 14 of the study using a computer-operated spirometer. Analysis was based on a linear MMRM with change from Baseline in parameter as outcome; including treatment, visit, treatment by visit interaction, severity of airflow limitation at Baseline, blood eosinophils (%) at Baseline, time from start of current COPD exacerbation to first study treatment dosing, presence of cardiovascular comorbidities at Screening, and COPD exacerbation treatment at Screening as fixed effects, and Baseline value and Baseline by visit interaction as covariates. Baseline was defined as the last non-missing value collected before the first study treatment administration, including unscheduled assessments.

End point type	Secondary

End point timeframe:

Days 3, 10, and 14

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: litre(s)				
arithmetic mean (standard deviation)				
Day 3	0.026 (± 0.2118)	0.059 (± 0.2101)	0.063 (± 0.2392)	
Day 10	0.095 (± 0.2900)	0.071 (± 0.1995)	0.063 (± 0.2879)	
Day 14	0.047 (± 0.2627)	0.056 (± 0.2782)	0.056 (± 0.2670)	

Statistical analyses

No statistical analyses for this end point

Secondary: Normalisation Evaluation of FEV1 Over Time (Days 1 to 7, Days 10 and 14, and Weeks 8, 12 and 26) Compared With the Most Recent Test Performed Within the Last 12 Months Outside an Exacerbation - ITT Population

End point title	Normalisation Evaluation of FEV1 Over Time (Days 1 to 7, Days 10 and 14, and Weeks 8, 12 and 26) Compared With the Most Recent Test Performed Within the Last 12 Months Outside an Exacerbation - ITT Population

End point description:

FEV1 data were recorded daily from Days 1 to 7 and on Days 10 and 14 and Weeks 8, 12, and 26 of the study using a computer-operated spirometer. FEV1 normalisation was achieved if FEV1 returned to a value ≥ 89% of the most recent FEV1 value measured within the last 12 months outside an exacerbation (pre-study FEV1 value). Baseline was defined as the last non-missing value collected before the first study treatment administration, including unscheduled assessments. Percentages (%) were based on number of non-missing values as denominator.

End point type	Secondary

End point timeframe:

Baseline, Days 1 to 7, Days 10 and 14, Week 8, Week 12, and Week 26.

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: percentage of participants				
number (not applicable)				
Baseline	67.9	59.3	64.6	
Day 2	61.9	65.2	73.2	
Day 3	67.5	62.6	75.0	

Day 4	62.7	65.9	75.0	
Day 5	71.1	70.2	74.7	
Day 6	76.8	70.5	75.0	
Day 7	71.6	71.6	70.4	
Day 10	77.2	65.9	66.7	
Day 14	69.1	61.6	75.3	
Week 8	74.0	65.4	71.4	
Week 12	70.5	63.0	68.8	
Week 26	75.7	67.1	69.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Normalisation Evaluation of FEV1/FVC Over Time (Days 1 to 7, Days 10 and 14, and Weeks 8, 12 and 26) Compared With the Most Recent Test Performed Within the Last 12 Months Outside an Exacerbation - ITT Population

End point title	Normalisation Evaluation of FEV1/FVC Over Time (Days 1 to 7, Days 10 and 14, and Weeks 8, 12 and 26) Compared With the Most Recent Test Performed Within the Last 12 Months Outside an Exacerbation - ITT Population

End point description:

FEV1 and FVC were recorded daily from Days 1 to 7 and on Days 10 and 14 and Weeks 8, 12, and 26 of the study using a computer-operated spirometer. FEV1/FVC normalisation was achieved if FEV1/FVC returned to a value ≥ 89% of the most recent FEV1/FVC value measured within the last 12 months outside an exacerbation (pre-study FEV1/FVC value). Baseline was defined as the last non-missing value collected before the first study treatment administration, including unscheduled assessments.

End point type	Secondary

End point timeframe:

Days 1 to 7, Days 10 and 14, Week 8, Week 12, and Week 26.

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: percentage of participants				
number (not applicable)				
Baseline	49.4	47.8	45.8	
Day 2	51.8	50.0	55.4	
Day 3	54.9	53.3	50.6	
Day 4	53.7	48.8	51.9	
Day 5	57.3	47.0	48.8	
Day 6	51.9	50.6	51.9	
Day 7	53.8	51.7	51.2	
Day 10	52.6	47.1	46.3	
Day 14	50.0	48.2	47.6	
Week 8	53.9	46.3	51.3	
Week 12	51.9	43.8	51.3	

Week 26	54.8	47.4	51.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement of 100 mL in FEV1 Over Time - ITT Population

End point title	Time to Improvement of 100 mL in FEV1 Over Time - ITT Population

End point description:

Time to improvement of 100 mL in FEV1 was defined as time (in days) from initiation of study treatment until the change in FEV1 was ≥ +100 mL.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: day				
median (confidence interval 95%)	3.0 (2.0 to 5.0)	2.0 (2.0 to 4.0)	4.0 (2.0 to 9.0)	

Statistical analyses

Statistical analysis title	Analysis of High Dose regimen vs Placebo

Statistical analysis description:

Log-rank comparison between treatment regimens.

Comparison groups	BCT197 High Dose Regimen - ITT Population v Placebo - ITT Population
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.399
Method	Logrank

Statistical analysis title	Analysis of Low Dose regimen vs Placebo

Statistical analysis description:

Log-rank comparison between treatment regimens.

Comparison groups	BCT197 Low Dose Regimen - ITT Population v Placebo - ITT Population
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.091
Method	Logrank

Statistical analysis title	Analysis of High vs Low Dose regimen
Statistical analysis description:	
Log-rank comparison between treatment regimens.	
Comparison groups	BCT197 High Dose Regimen - ITT Population v BCT197 Low Dose Regimen - ITT Population
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.437
Method	Logrank

Secondary: AUC of FEV1 Over Time - ITT Population

End point title	AUC of FEV1 Over Time - ITT Population
End point description:	
AUC was calculated according to the trapezoidal rule. The trapezoidal rule is a numerical method to be used to approximate the integral or the area under a curve. Using trapezoidal rule to approximate the area under a curve first involves dividing the area into a number of strips of equal width. Then, approximating the area of each strip by the area of the trapezium formed when the upper end is replaced by a chord. The sum of these approximations gives the final numerical result of the AUC.	
End point type	Secondary
End point timeframe:	
Day 1 to Day 14	

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: mg/(mL*min)				
arithmetic mean (standard deviation)				
Day 1-3	1.207 (± 0.4090)	1.111 (± 0.4245)	1.097 (± 0.3876)	
Day 1-7	1.232 (± 0.4296)	1.143 (± 0.4433)	1.108 (± 0.3980)	
Day 1-10	1.263 (± 0.4934)	1.174 (± 0.4380)	1.155 (± 0.4061)	
Day 1-14	1.293 (± 0.4743)	1.192 (± 0.4007)	1.125 (± 0.4293)	

Statistical analyses

No statistical analyses for this end point

Secondary: Normalisation of Respiratory Rate (RR) Over Time During Acute Exacerbation Phase - ITT Population

End point title	Normalisation of Respiratory Rate (RR) Over Time During Acute Exacerbation Phase - ITT Population

End point description:

RR was normalised when it returned to a baseline plateau level achieved after the acute COPD exacerbation during the Stabilization Phase. Baseline was defined as the last non-missing value collected before the first study treatment administration, including unscheduled assessments.

End point type	Secondary

End point timeframe:

Day 1 to Day 14

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: percentage of participants				
number (not applicable)				
Baseline	14.9	20.4	17.4	
Day 2	28.7	26.9	26.7	
Day 3	28.7	39.8	29.4	
Day 4	37.9	45.1	37.6	
Day 5	41.4	52.7	39.3	
Day 6	44.8	48.4	48.2	
Day 7	51.2	51.6	47.1	
Day 10	47.6	60.4	48.2	
Day 14	57.8	52.3	56.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in RR on Days 3, 7, 10 and 14 - ITT Population

End point title	Change From Baseline in RR on Days 3, 7, 10 and 14 - ITT Population

End point description:

RR (breaths/min) was recorded over time during the acute exacerbation phase.

End point type	Secondary

End point timeframe:

Days 1 to 14

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: breaths/min				
median (full range (min-max))				
Day 3	-2.0 (-8.0 to 3.0)	-1.0 (-8.0 to 5.0)	-2.0 (-8.0 to 2.0)	
Day 7	-3.0 (-13.0 to 8.0)	-2.0 (-13.0 to 4.0)	-2.0 (-12.0 to 1.0)	
Day 10	-3.0 (-13.0 to 4.0)	-2.0 (-14.0 to 4.0)	-2.0 (-12.0 to 2.0)	
Day 14	-3.0 (-13.0 to 4.0)	-2.0 (-16.0 to 6.0)	-3.0 (-12.0 to 1.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement Based on the EXAcerbations of Chronic Pulmonary Disease Tool (EXACT) - Patient Reported Outcome (PRO) Total Score During the Acute Exacerbation Phase - ITT Population

End point title	Time to Improvement Based on the EXAcerbations of Chronic Pulmonary Disease Tool (EXACT) - Patient Reported Outcome (PRO) Total Score During the Acute Exacerbation Phase - ITT Population

End point description:

Improvement based on EXACT-PRO total score is defined as a decrease in the Rolling Average EXACT score ≥ 9 points from the previous day's maximum observed value during an event. The EXACT is a 14-item PRO daily diary used to quantify and measure exacerbations of COPD. The health status of the participant is correlated to the global score, meaning a higher score corresponds to a more severe health status of the participant. An EXACT total score is computed for each day of diary collection. The EXACT total score is based on a logit scoring system with conversion to a 0 to 100 scale for ease of interpretation and use. The total score was used in the determination of exacerbation frequency, severity, and duration of exacerbation. Specifically, changes in the total score were used to define onset and recovery from an exacerbation event and the magnitude of that event. 999 = Insufficient data to evaluate the upper or lower limit.

End point type	Secondary

End point timeframe:

Days 1 to 29

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: day				
median (confidence interval 95%)	5.0 (3.0 to 16.0)	6.0 (3.0 to 999)	5.0 (3.0 to 7.0)	

Statistical analyses

Statistical analysis title	Analysis of High Dose Regimen vs Placebo
Statistical analysis description:	
Log-rank comparison between treatment regimens.	
Comparison groups	BCT197 High Dose Regimen - ITT Population v Placebo - ITT Population
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	Logrank

Statistical analysis title	Analysis of Low Dose Regimen vs Placebo
Statistical analysis description:	
Log-rank comparison between treatment regimens.	
Comparison groups	BCT197 Low Dose Regimen - ITT Population v Placebo - ITT Population
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.298
Method	Logrank

Statistical analysis title	Analysis of High vs Low Dose Regimen
Statistical analysis description:	
Log-rank comparison between treatment regimens.	
Comparison groups	BCT197 High Dose Regimen - ITT Population v BCT197 Low Dose Regimen - ITT Population
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Logrank

Secondary: Time to Recovery Based on EXACT-PRO Total Score During the Acute Exacerbation Phase - ITT Population

End point title	Time to Recovery Based on EXACT-PRO Total Score During the Acute Exacerbation Phase - ITT Population

End point description:

Recovery based on EXACT-PRO total score was defined as the first day in which a participant experiences a persistent, sustained improvement in their condition over the observed period (Day 1 to Day 29). Improvement had to be present for 7 consecutive days. The first day of the 7-day period was designated as the first day of Recovery. An EXACT total score was computed for each day of diary collection. CI: 0 to 999 = Insufficient data to evaluate the upper or lower limit.

End point type	Secondary

End point timeframe:

Days 1 to 29

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: days				
median (confidence interval 95%)	6.0 (0 to 999)	6.0 (0 to 999)	6.0 (6.0 to 7.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Standardised AUC of EXACT-PRO Rolling Average Over Time During Acute Exacerbation Phase - ITT Population

End point title	Standardised AUC of EXACT-PRO Rolling Average Over Time During Acute Exacerbation Phase - ITT Population

End point description:

The standardised AUC of the EXACT-PRO were calculated from Day (a) to Day (b) using the trapezoidal rule.

End point type	Secondary

End point timeframe:

Days 1 to 29

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: mg/(mL*min)				
median (full range (min-max))				
Day 1-7	45.389 (20.58 to 64.94)	44.736 (19.61 to 63.19)	43.938 (19.00 to 67.75)	
Day 1-14	42.641 (21.81 to 63.38)	42.250 (22.80 to 64.87)	42.590 (17.74 to 65.42)	
Day 1-29	41.470 (19.43 to 62.92)	40.932 (19.81 to 65.25)	41.652 (20.35 to 61.27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Standardised AUC of EXACT-PRO (Breathlessness) Rolling Average Over Time During Acute Exacerbation Phase - ITT Population

End point title	Standardised AUC of EXACT-PRO (Breathlessness) Rolling Average Over Time During Acute Exacerbation Phase - ITT Population

End point description:

Information regarding the participant's condition can be obtained through 3 domain scores embedded within the EXACT measure: Breathlessness, Cough and Sputum, and Chest Symptoms. These scores also range from 0 to 100 with higher scores indicating more severe symptoms. The standardised AUC of the EXACT-PRO were calculated from Day (a) to Day (b) using the trapezoidal rule.

End point type	Secondary

End point timeframe:

Days 1 to 29

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: mg/(mL*min)				
median (full range (min-max))				
Day 1-7	50.083 (21.58 to 80.00)	47.861 (15.58 to 78.00)	47.556 (13.13 to 85.50)	
Day 1-14	45.417 (21.27 to 79.65)	45.577 (20.60 to 77.73)	44.436 (17.41 to 80.69)	
Day 1-29	44.911 (23.27 to 79.41)	45.315 (17.84 to 77.63)	43.387 (18.65 to 74.91)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Positively Adjudicated Moderate/Severe COPD Exacerbations - ITT Population

End point title	Rate of Positively Adjudicated Moderate/Severe COPD Exacerbations - ITT Population

End point description:

Follow-up time per participant (years) was defined as (date of last contact - date of first study drug administration + 1)/ 365.25. Total follow-up time (years) = sum of individual participant follow-up times. Rate was calculated as total number of positively adjudicated exacerbations divided by the total follow-up time in years of the treatment group.

End point type	Secondary

End point timeframe:

Day 1 to end of study

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: per patient per year				
number (not applicable)	0.744	0.921	0.904	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of COPD-Related Deaths During the Study - ITT Population

End point title	Number of COPD-Related Deaths During the Study - ITT Population

End point description:

Cumulative incidences of COPD-related deaths until Day 30/60/90/120/150/180 were obtained.

End point type	Secondary

End point timeframe:

Days 1 to 180

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: participants				
Until Day 30	0	0	1	
Until Day 60	0	0	1	

Until Day 90	0	0	1	
Until Day 120	0	0	1	
Until Day 150	1	0	1	
Until Day 180	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Positively Adjudicated Moderate/Severe COPD Exacerbation- ITT Population

End point title	Time to Next Positively Adjudicated Moderate/Severe COPD Exacerbation- ITT Population

End point description:

Time to next positively adjudicated moderate/severe COPD exacerbation (in days) was defined as date when first moderate/severe COPD exacerbation symptoms started - date when current COPD exacerbation symptoms stopped, where COPD exacerbations experienced during the study were positively adjudicated by the Independent Adjudication Committee. Time to next positively adjudicated COPD exacerbation was presented in 25th percentile (95% CI) as medians were not evaluable. 999 = Insufficient data to evaluate the upper or lower limit.

End point type	Secondary

End point timeframe:

Day 1 to date of next COPD exacerbation after entering the study, withdrawal or last contact date, or death date

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: days				
median (confidence interval 95%)	168.0 (70.0 to 999)	75.0 (45.0 to 136.0)	143.0 (48.0 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Hospitalisation Admission Until the Participant Is Medically Ready for Discharge (Current COPD) - ITT Population

End point title	Time From Hospitalisation Admission Until the Participant Is Medically Ready for Discharge (Current COPD) - ITT Population

End point description:

Time from hospitalisation admission until the participant is medically ready for discharge (in days) = Date participant was medically ready for discharge from hospital - Date of hospitalisation admission. 'Date of hospitalisation admission' and 'Date participant was medically ready for discharge from hospital' were recorded on the 'Current COPD Exacerbation' form of the electronic case report form. Results were presented with 75th percentile (95% CI) due to the fact that 95% CI for the median was not evaluable.

End point type	Secondary

End point timeframe:

Date of hospital admission to date medically ready for discharge by investigator judgement

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: days				
median (confidence interval 95%)	9.0 (8.0 to 12.0)	9.0 (8.0 to 13.0)	9.0 (8.0 to 10.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Days With Intake of COPD Rescue Therapy - ITT Population

End point title	Percentage of Days With Intake of COPD Rescue Therapy - ITT Population

End point description:

Participants completed the EXACT-PRO starting from Day 1 and recorded rescue medication use and any occurrences of COPD once a day (evening) in the diary. The percentage of days with intake of rescue medications was evaluated on the basis of the information recorded daily by the participant on the diaries. A day was considered with intake of rescue medications if the answer to the question "How many puffs of rescue medication did you take since last evening?" was> 0.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: days				
arithmetic mean (standard deviation)				
Acute Exacerbation Phase (Overall)	73.28 (± 32.721)	71.90 (± 33.565)	69.65 (± 35.674)	
Stabilization Phase (Overall)	70.78 (± 37.122)	71.08 (± 40.299)	67.35 (± 38.953)	

Statistical analyses

No statistical analyses for this end point

Secondary: Standardised AUC of EXACT-PRO (Cough and Sputum) Rolling Average Over Time During Acute Exacerbation Phase - ITT Population

End point title	Standardised AUC of EXACT-PRO (Cough and Sputum) Rolling Average Over Time During Acute Exacerbation Phase - ITT Population

End point description:

Information regarding the participant's condition can be obtained through 3 domain scores embedded within the EXACT measure: Breathlessness, Cough and Sputum, and Chest Symptoms. These scores also range from 0 to 100 with higher scores indicating more severe symptoms. The standardised AUC of the EXACT-PRO were calculated from Day (a) to Day (b) using the trapezoidal rule.

End point type	Secondary

End point timeframe:

Days 1 to 29

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: mg/(mL*min)				
median (full range (min-max))				
Day 1-7	36.792 (14.00 to 61.81)	39.000 (13.00 to 71.97)	39.035 (20.58 to 65.17)	
Day 1-14	33.077 (16.31 to 55.35)	36.006 (17.46 to 77.91)	34.397 (16.50 to 66.59)	
Day 1-29	33.467 (18.46 to 59.23)	35.155 (16.36 to 70.85)	32.086 (17.63 to 61.58)	

Statistical analyses

No statistical analyses for this end point

Secondary: Standardised AUC of EXACT-PRO (Chest Symptoms) Rolling Average Over Time During Acute Exacerbation Phase - ITT Population

End point title	Standardised AUC of EXACT-PRO (Chest Symptoms) Rolling Average Over Time During Acute Exacerbation Phase - ITT Population

End point description:

Information regarding the participant's condition can be obtained through 3 domain scores embedded within the EXACT measure: Breathlessness, Cough and Sputum, and Chest Symptoms. These scores also range from 0 to 100 with higher scores indicating more severe symptoms. The standardised AUC of the EXACT-PRO were calculated from Day (a) to Day (b) using the trapezoidal rule.

End point type	Secondary

End point timeframe:

Days 1 to 29

End point values	BCT197 High Dose Regimen - ITT Population	BCT197 Low Dose Regimen - ITT Population	Placebo - ITT Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	86	
Units: mg/(mL*min)				
median (full range (min-max))				
Day 1-7	41.069 (17.25 to 66.75)	38.583 (12.00 to 65.38)	40.722 (12.00 to 69.08)	
Day 1-14	37.446 (14.42 to 64.54)	36.330 (12.14 to 66.52)	38.301 (12.00 to 67.46)	
Day 1-29	37.717 (13.13 to 65.65)	36.012 (13.62 to 68.75)	37.750 (15.06 to 61.17)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PK of BCT197 in Adults With COPD – PK Population

End point title	PK of BCT197 in Adults With COPD – PK Population
End point description:	
Descriptive summary of PK plasma concentration is presented as no-specific PK report is available.	
End point type	Other pre-specified
End point timeframe:	
Days 1 to 5	

End point values	BCT197 High Dose Regimen - PK Population	BCT197 Low Dose Regimen - PK Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	92		
Units: ng/mL				
geometric mean (confidence interval 95%)				
Day 1 (0-2 h post-dose)	97.40 (65.13 to 145.66)	75.98 (47.81 to 120.73)		
Day 1 (4-8h post dose)	387.65 (343.22 to 437.83)	283.79 (261.28 to 308.25)		
Day 1 (>12h post-dose)	413.85 (376.28 to 455.17)	286.40 (267.20 to 306.97)		
Day 3 (predose)	271.10 (251.34 to 292.41)	161.13 (147.69 to 175.80)		

Day 3 (0-2h post-dose)	318.88 (290.57 to 349.95)	184.46 (165.72 to 205.31)		
Day 3 (4-8h post-dose)	496.31 (457.30 to 538.64)	299.79 (281.99 to 318.71)		
Day 3 (>12h post-dose)	466.86 (434.70 to 501.40)	249.60 (231.21 to 269.46)		
Day 5 (predose)	272.43 (246.62 to 300.95)	128.38 (111.99 to 147.17)		
Day 5 (0-2h post-dose)	310.20 (277.37 to 346.91)	155.10 (130.77 to 183.94)		
Day 5 (4-8h post-dose)	504.53 (453.33 to 561.52)	278.73 (246.56 to 315.10)		
Day 5 (>12h post-dose)	465.28 (423.05 to 511.72)	240.31 (215.77 to 267.63)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from signing the informed consent form to completion of the 26 week follow-up period after the last administration of study drug.

Adverse event reporting additional description:

Serious AEs are also included in the non-serious AE section as a non-serious AE table was not available.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	BCT197 High Dose Regimen

Reporting group description:

Participants received 75 mg BCT197 orally on Day 1. Subsequent doses with 40 mg BCT197 were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.

Reporting group title	BCT197 Low Dose Regimen

Reporting group description:

Participants received 40 mg BCT197 orally on Day 1. Subsequent doses with 20 mg BCT197 were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.

Reporting group title	Placebo

Reporting group description:

Participants received placebo orally on Day 1. Subsequent doses with placebo were administered orally on Day 3 and Day 5. All participants also received SoC treatment for the acute exacerbation of COPD.

Serious adverse events	BCT197 High Dose Regimen	BCT197 Low Dose Regimen	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 92 (18.48%)	27 / 96 (28.13%)	29 / 91 (31.87%)
number of deaths (all causes)	2	3	2
number of deaths resulting from adverse events	2	3	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal cancer			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Angina unstable			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (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
Atrial fibrillation			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (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
Cardiopulmonary failure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Apallic syndrome			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal wall haematoma			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (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
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
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			
Bronchiectasis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
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	13 / 92 (14.13%)	21 / 96 (21.88%)	22 / 91 (24.18%)
occurrences causally related to treatment / all	0 / 14	0 / 28	0 / 25
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Chronic respiratory failure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (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
Pulmonary embolism			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary fibrosis			

subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (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 failure			
subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	3 / 91 (3.30%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (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
Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (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
Infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (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
Pneumonia			
subjects affected / exposed	1 / 92 (1.09%)	3 / 96 (3.13%)	2 / 91 (2.20%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Viral infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (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
Metabolism and nutrition disorders			

Diabetes mellitus			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	BCT197 High Dose Regimen	BCT197 Low Dose Regimen	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 92 (60.87%)	63 / 96 (65.63%)	62 / 91 (68.13%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Basal cell carcinoma			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Laryngeal cancer			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Lung neoplasm malignant			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Phaeochromocytoma			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Prostate cancer			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Vascular disorders			

Aortic aneurysm			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Aortic arteriosclerosis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Circulatory collapse			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	4 / 92 (4.35%)	2 / 96 (2.08%)	4 / 91 (4.40%)
occurrences (all)	5	2	4
Hypertensive crisis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	2 / 91 (2.20%)
occurrences (all)	0	0	2
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 92 (2.17%)	0 / 96 (0.00%)	3 / 91 (3.30%)
occurrences (all)	2	0	3
Chest discomfort			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	2 / 92 (2.17%)	1 / 96 (1.04%)	1 / 91 (1.10%)
occurrences (all)	2	1	1
Chills			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Death			

subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Extravasation			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Generalised oedema			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	1 / 91 (1.10%)
occurrences (all)	0	1	1
Peripheral swelling			
subjects affected / exposed	0 / 92 (0.00%)	2 / 96 (2.08%)	0 / 91 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast disorders			
Vulvovaginal inflammation			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Bronchospasm			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	24 / 92 (26.09%)	32 / 96 (33.33%)	28 / 91 (30.77%)
occurrences (all)	33	42	41
Chronic respiratory failure			

subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	3 / 92 (3.26%)	2 / 96 (2.08%)	4 / 91 (4.40%)
occurrences (all)	3	2	5
Emphysema			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	2 / 92 (2.17%)	0 / 96 (0.00%)	2 / 91 (2.20%)
occurrences (all)	2	0	2
Haemoptysis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Hypoxia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	1 / 91 (1.10%)
occurrences (all)	0	1	1
Paranasal cyst			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Pleural thickening			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	1	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Pulmonary fibrosis			

subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Pulmonary hypertension			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Rales			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	1	0	1
Respiratory failure			
subjects affected / exposed	1 / 92 (1.09%)	2 / 96 (2.08%)	3 / 91 (3.30%)
occurrences (all)	1	2	3
Rhinorrhoea			
subjects affected / exposed	2 / 92 (2.17%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	2	0	0
Tonsillar erythema			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Upper respiratory tract congestion			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	2 / 92 (2.17%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	2	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 92 (0.00%)	2 / 96 (2.08%)	0 / 91 (0.00%)
occurrences (all)	0	2	0
Depression			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Dysphoria			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	3 / 92 (3.26%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	3	0	1

Sleep disorder			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 92 (3.26%)	3 / 96 (3.13%)	2 / 91 (2.20%)
occurrences (all)	3	4	2
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 92 (1.09%)	4 / 96 (4.17%)	1 / 91 (1.10%)
occurrences (all)	1	5	1
Blood creatinine increased			
subjects affected / exposed	0 / 92 (0.00%)	2 / 96 (2.08%)	0 / 91 (0.00%)
occurrences (all)	0	4	0
Blood glucose increased			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	1	0	1
Blood phosphorus decreased			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	2 / 91 (2.20%)
occurrences (all)	1	0	2
Blood potassium increased			
subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	1 / 91 (1.10%)
occurrences (all)	1	1	1
Blood pressure increased			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Blood urea increased			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Blood uric acid increased			
subjects affected / exposed	2 / 92 (2.17%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	2	0	1
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 92 (0.00%)	3 / 96 (3.13%)	0 / 91 (0.00%)
occurrences (all)	0	3	0
Gamma-glutamyltransferase abnormal			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 92 (2.17%)	2 / 96 (2.08%)	1 / 91 (1.10%)
occurrences (all)	2	2	1
Haemoglobin decreased			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	2	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
International normalised ratio increased			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Monocyte count increased			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	1	0	1
Platelet count increased			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Protein total decreased			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Prothrombin time prolonged			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Troponin I increased			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Weight decreased			

subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Hand fracture			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	1	1	0
Tendon injury			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Upper limb fracture			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Angina unstable			
subjects affected / exposed	0 / 92 (0.00%)	2 / 96 (2.08%)	0 / 91 (0.00%)
occurrences (all)	0	2	0
Atrial fibrillation			

subjects affected / exposed	3 / 92 (3.26%)	2 / 96 (2.08%)	1 / 91 (1.10%)
occurrences (all)	3	2	1
Atrial tachycardia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Bundle branch block left			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Cardiac aneurysm			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Cardiac failure			
subjects affected / exposed	1 / 92 (1.09%)	2 / 96 (2.08%)	2 / 91 (2.20%)
occurrences (all)	1	2	2
Cardiac failure acute			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Cardiac failure chronic			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Cardiac failure congestive			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Cardiopulmonary failure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Cor pulmonale			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Intracardiac thrombus			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Myocardial ischaemia			

subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Right ventricular failure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Sinus bradycardia			
subjects affected / exposed	0 / 92 (0.00%)	2 / 96 (2.08%)	0 / 91 (0.00%)
occurrences (all)	0	2	0
Sinus tachycardia			
subjects affected / exposed	2 / 92 (2.17%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	2	0	0
Supraventricular extrasystoles			
subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	1	1	0
Tachyarrhythmia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	1	1	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	2 / 91 (2.20%)
occurrences (all)	0	1	2
Ventricular tachycardia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	2 / 91 (2.20%)
occurrences (all)	0	0	2
Nervous system disorders			
Apallic syndrome			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Arachnoid cyst			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Brain oedema			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1

Coma			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	2	0	0
Epilepsy			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	3 / 92 (3.26%)	1 / 96 (1.04%)	1 / 91 (1.10%)
occurrences (all)	3	1	1
Hypotonia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	3 / 92 (3.26%)	2 / 96 (2.08%)	0 / 91 (0.00%)
occurrences (all)	4	2	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Leukocytosis			
subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	1	1	0
Leukopenia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Lymphadenopathy mediastinal			

subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Lymphocytosis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Lymphopenia			
subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	1 / 91 (1.10%)
occurrences (all)	1	1	1
Neutropenia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	1	0	1
Thrombocytosis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	1	0	2
Eye disorders			
Chalazion			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Retinal vein occlusion			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Scleral hyperaemia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Vitreous detachment			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			

subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Abdominal wall haematoma			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	4 / 91 (4.40%)
occurrences (all)	1	0	4
Dyspepsia			
subjects affected / exposed	0 / 92 (0.00%)	4 / 96 (4.17%)	0 / 91 (0.00%)
occurrences (all)	0	6	0
Gastric polyps			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	1	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Pancreatitis chronic			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Cholecystitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Cholelithiasis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0

Drug-induced liver injury			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Hepatic steatosis			
subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	1 / 91 (1.10%)
occurrences (all)	1	1	1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Liver injury			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Non-alcoholic fatty liver			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Decubitus ulcer			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Dermatitis acneiform			
subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	1	1	0
Dermatitis allergic			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			

subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Pemphigoid			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Skin ulcer			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	1 / 91 (1.10%)
occurrences (all)	0	1	1
Diabetic nephropathy			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	2	0
Haematuria			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Renal artery stenosis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Renal colic			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Renal cyst			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Urinary incontinence			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 92 (2.17%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	2	1	0
Bone swelling			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Spinal osteoarthritis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	2	0	0
Chronic sinusitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	2
Conjunctivitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Infection			

subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	1	0	1
Laryngitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	1 / 91 (1.10%)
occurrences (all)	1	1	1
Mastoiditis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	4 / 92 (4.35%)	4 / 96 (4.17%)	2 / 91 (2.20%)
occurrences (all)	4	4	2
Oesophageal candidiasis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	1	0	1
Oral herpes			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	3 / 92 (3.26%)	3 / 96 (3.13%)	2 / 91 (2.20%)
occurrences (all)	3	3	2
Respiratory tract infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection viral			
subjects affected / exposed	3 / 92 (3.26%)	3 / 96 (3.13%)	0 / 91 (0.00%)
occurrences (all)	3	3	0
Sepsis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	2
Sinusitis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	2 / 91 (2.20%)
occurrences (all)	1	0	2
Upper respiratory tract infection			

subjects affected / exposed	1 / 92 (1.09%)	1 / 96 (1.04%)	1 / 91 (1.10%)
occurrences (all)	1	1	1
Viral infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 96 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Dehydration			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	2 / 91 (2.20%)
occurrences (all)	0	0	2
Diabetes mellitus			
subjects affected / exposed	2 / 92 (2.17%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	2	0	1
Dyslipidaemia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Glucose tolerance impaired			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	2 / 92 (2.17%)	4 / 96 (4.17%)	2 / 91 (2.20%)
occurrences (all)	2	4	3
Hyperkalaemia			
subjects affected / exposed	1 / 92 (1.09%)	2 / 96 (2.08%)	1 / 91 (1.10%)
occurrences (all)	2	3	1
Hypochloraemia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	2 / 92 (2.17%)	1 / 96 (1.04%)	1 / 91 (1.10%)
occurrences (all)	2	1	1

Hyponatraemia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	2 / 91 (2.20%)
occurrences (all)	0	0	2
Hypoproteinaemia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 96 (1.04%)	0 / 91 (0.00%)
occurrences (all)	0	1	0
Obesity			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	1 / 91 (1.10%)
occurrences (all)	0	0	1
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 92 (0.00%)	0 / 96 (0.00%)	2 / 91 (2.20%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 December 2015	Changes were made to the original protocol at the request of the Food and Drug Administration (FDA). These included the removal of the caveat that increased creatinine or proteinuria was a discontinuation criterion unless it was due to disease progression, amendment of liver laboratory values requiring study drug discontinuation to be consistent with the FDA Drug-induced Liver Injury Premarketing Clinical Evaluation, the addition of pulse oximeter measurements was to be carried out as part of vital sign measurements. Administrative changes were also included.
10 March 2016	Amendments as required by the United Kingdom Regulatory Agency included the removal of the method of contraception under the heading "highly effective" that was not so defined in the Clinical Trials Facilitation Group guidance document, introduction of a discontinuation criterion of change in Baseline corrected QT interval by Fredericia (QTcF) ≥ 60 msec, clarification of study stopping criteria to include stopping the study at the request of the Data Monitoring Committee, definition of End of Study was added, and addition of inflammation of cervix and vagina as an adverse event of special interest to be in line with the Investigator's Brochure. Other changes included the requirement for the initial blood sample to be collected when the subject was in a fasting state being waived due to the nature of the disease and the need to begin treatment as soon as possible, clarification provided that spirometry testing carried out at Visit 2 were used for the body mass index, airflow obstruction, dyspnoea and exercise index at Day 1 if the subject was randomised based on previous spirometry, the requirement for international normalised ratio and prothrombin time sampling and testing after Day 14 was removed as there was no systemic study drug exposure beyond that time, and reduction of electrocardiogram testing from triplicate to a single test. Clarification provided that barrier contraception was only required during the dosing period and for 5 half-lives (8 days) afterwards and that azithromycin was a prohibited medication. Other clarifications, administrative changes, and corrections of typographical errors were made.
26 May 2016	Changes included modification of inclusion/exclusion criteria, modifications of clinical and laboratory assessments, revision of the time frame for permitted concomitant medications, addition of theophylline to permitted concomitant medications, modification of rescue medication use, the medically fit for discharge endpoint was further clarified from a COPD perspective, suspected unexpected serious adverse reaction reporting to regulatory and ethics committees was added, the number of countries was updated from 'approximately 8' to 'approximately 12' and correction of previous clinical dosing from 14 weeks to 14 days. Administrative changes were also included.
08 November 2016	The following updates were made: clarification that the P-gp inhibitor azithromycin was not prohibited following results from a drug interaction study (Study MBCT102), removal of the use of killed vaccine within the last 14 days from exclusion criterion 10 as not considered a safety risk (exclusion limited to live vaccines), removal of killed vaccine from the list of prohibited medications as not considered a safety risk (exclusion limited to live vaccines), protocol guidance that if vaccine was given 14 days prior to, or concomitant with study drug, consideration should have been given to checking vaccine responses and/or revaccinating, visit descriptions were updated to be consistent with the schedule of assessments, removal of oral requirement for body temperature, removal of exclusion criterion 7 because long-term oxygen therapy was not prohibited since protocol amendment 3.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported