# 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 | - | - |
| Consent withdrawn by subject | 5 | 8 | 2 |
| Physician decision | 1 | - | - |
| 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<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 63.8 | 63.3 | 64.9 |
| standard deviation | ± 8.21 | ± 8.68 | ± 7.34 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 24 | 28 | 30 |
| Male | 68 | 68 | 61 |
| Race/Ethnicity<br>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)<br>arithmetic mean<br>standard deviation | -<br> | | |
| 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)<br>arithmetic mean<br>standard deviation | -<br> | | |

## 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

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| 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.

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| 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.

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| 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 |

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|---|---|---|---|
| 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 |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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