1 TITLE PAGE

CLINICAL STUDY PROTOCOL

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

Protocol No.: MBCT206	EUDRACT No.: 2015-004631-13
Test Product:	BCT197
Indication:	Acute exacerbations of chronic obstructive pulmonary disease
Sponsor:	Mereo BioPharma 1 Ltd
Development Phase:	Phase IIa
Sponsor Signatory:	Dr Alastair Mackinnon
Sponsor Medical Expert:	Dr Jackie Parkin
Date of the Protocol:	08 November 2016
Version of the Protocol:	Final 5.0

2 SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: 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

PROTOCOL NUMBER: MBCT206

Mereo BioPharma 1 Limited

[redacted]

08th NOVEMBER 2016
Date (day/month/year)

3 GENERAL INFORMATION

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

Protocol No.:	MBCT206
Date of the Protocol:	26 May 2016
Date and Number of Amendment(s):	23 December 2015, Amendment 1 10 March 2016, Amendment 2 26 May 2016, Amendment 3
Sponsor:	Mereo BioPharma 1 Ltd 4th Floor 1 Cavendish Place London W1G 0QF UK
Clinical Research Organisation:	ICON Clinical Research Ltd South County Business Park Leopardstown Dublin 18 Ireland
Sponsor Signatory:	[redacted] 4th Floor 1 Cavendish Place London W1G 0QF UK Tel No.: +44 (0)3330 237314 Fax No.: +44 (0)3330 237301
Sponsor Medical Expert:	[redacted] Mereo BioPharma 1 Ltd 4th Floor 1 Cavendish Place London W1G 0QF UK Tel No.: +44 (0)3330 237320 Fax No.: +44 (0)3330 237301
Principal Investigator:	Prof Wisia Wedzicha Professor of Respiratory Medicine National Heart and Lung Institute Imperial College London
Biostatistics:	[redacted] rch UK Ltd 2 Globeside Business Park Marlow Buckinghamshire UK Tel No.: +44 (0)1628 493520

4 STUDY SYNOPSIS

Name of Sponsor/Company: Mereo BioPharma 1 Ltd	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Product: BCT197		
Name of Active Ingredient: 3-[5-Amino-4-(3-cyano-benzoyl)-pyrazol-1-yl]-Ncyclopropyl-4-methyl-benzamid	**Volume:** **Page:**	

Title of Study:

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

Study Centres:

It is planned that approximately 90 centres will be initiated for this study in approximately 12 countries worldwide.

Publications:

None.

Development Phase:

Phase IIa

Objectives:

Primary Objective:

1. 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.

Secondary Objectives:

The secondary objectives are to evaluate the efficacy and tolerability of two different dosing regimens of BCT197 added to SoC versus placebo added to SoC in treatment of an acute exacerbation of COPD requiring hospitalisation by measuring the following:

1. Comparison of FEV1 on Days 3, 10, and 14
2. Normalisation evaluation of spirometry parameter (FEV1, forced vital capacity [FVC], and FEV1/FVC) response over time (performed daily from Days 1 to 7, 10, and 14, and Weeks 8, 12 and 26) compared with the most recent test performed within the last 12 months outside an exacerbation (pre-study FEV1, FVC, and FEV1/FVC value)
3. Time taken to improvement of 100 mL in FEV1 compared to Baseline versus placebo
4. Assessment of AUC of FEV1 over time among groups
5. Respiratory rate (RR) normalisation over time (performed daily from Days 1 to 7, 10, and 14) among groups
6. RR at Days 3, 7, 10, and 14 among groups
7. Time to improvement based on EXACT-PRO total score
8. Assessment of AUC of EXACT-PRO over time among groups
9. Evaluate the number of COPD-related deaths among groups
10. Evaluate the number of moderate/severe COPD exacerbations (classified according to European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) guidelines, refer to Section 11.2.3) over time among groups
11. Evaluate time to next moderate/severe COPD exacerbation
12. Change from Baseline at each inter-visit period and over the entire period of the study in the average EXACT-PRO total score and domain scores

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13. Evaluate the use of rescue therapy during the study
14. Evaluate time from hospitalisation until subject is medically ready (COPD-related) for discharge
15. To characterise the pharmacokinetics (PK) of BCT197 in adults with COPD.

Safety and tolerability of BCT197

1. Evaluation of each treatment emergent adverse event (TEAE)/serious adverse event (SAE) (from first dose of study drug until study completion)
2. Evaluation of the incidence of pneumonia from first dose of study drug until completion
3. TEAEs of special interest: rash, acneiform dermatitis, cervical/vaginal inflammation, headache, pruritus and liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin)
4. Evaluation of vital signs and laboratory parameters
5. Evaluation of QTc intervals overtime at Baseline, Day 1 to Day 7 (daily), Days 10 and 14
6. Quantitative sputum culture over Days 1 to 14 whenever sputum is collected for clinical purposes.

Exploratory Objectives

Exploratory assessments will evaluate:

1. Exploratory composite scale endpoints comparing among the three groups at Weeks 8, 12 and 26:
   - Number of events of worsening of symptoms warranting the addition of antibiotics
   - Number of events of worsening of symptoms warranting an increase of oral dose of corticosteroids or initiation of new oral corticosteroids
   - Number of events of worsening of symptoms requiring additional treatment with oral corticosteroids and/or antibiotics after completion of the initial regimen
   - Number of events of COPD exacerbations that required re-hospitalisation
   - Number of COPD-related deaths.
2. Chronic respiratory questionnaire (CRQ) at Baseline, Day 14 and at Weeks 8, 12 and 26 to evaluate recovery comparing among the three groups over time
3. Cumulative oral /intravenous (IV) steroid dose on Days 1 to 14, and from Day 14 to Week 26
4. Change in inflammatory blood biomarkers (IL-6, TNF-α, fibrinogen, high-sensitivity C-reactive protein [hs-CRP], and myeloperoxidase [MPO]) daily during Part 1 of the study, and at Weeks 8, 12 and 26
5. Explore the relationship between BCT197 exposure and efficacy/safety endpoints
6. Change from Baseline in modified Medical Research Council (mMRC) dyspnoea scale over time
7. Body mass index, airflow Obstruction, Dyspnoea and Exercise (BODE) index among the three groups at Day 14.

Methodology:

This is a two-part, randomised, multi-centre, multinational, double-blind, placebo-controlled, three arm study of BCT197 added to SoC (which includes at least steroids and/or antibiotics) in subjects with an acute respiratory exacerbation of COPD, which require hospitalisation (per the GOLD 2015 definition of exacerbation). As well as SoC, subjects will receive one of two oral dosing regimens of BCT197 or matching oral placebo administered according to the schedule in the following table:

[redacted]

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Subjects will only be eligible for Randomisation and study treatment if they present with an acute respiratory exacerbation of COPD requiring hospitalisation and meet all inclusionary criteria and none of the exclusionary criteria.

The study will consist of a Screening/Baseline visit starting the Acute Exacerbation Phase, followed by a Stabilisation Phase. After signing of informed consent, all subjects will be assessed for eligibility by confirming inclusion/exclusion criteria, randomised and receive their first dose of study treatment within 24 hours of presentation with acute exacerbation (Day 1). Subjects will be eligible only if their treatment (SoC) has been initiated less than 24 hours before Randomisation and dosing.

Subjects will be randomised to treatment on Day 1 and enter into Part 1 (Acute Exacerbation Phase) of the study. The Acute Exacerbation Phase includes efficacy and safety assessments for up to 14 days. Part 2 (Stabilisation Phase) begins after completion of the Acute Exacerbation Phase and includes visits at Weeks 8, 12 and 26. The subject's medical condition will be monitored at each visit and SoC medication adjusted as needed.

Assessments during Part 1 and Part 2 include:

1. Part 1 (Acute Exacerbation Phase): Inpatient hospitalisation and Randomisation which will include daily assessments of pulmonary function (FEV1 and RR) for the first 7 days of hospitalisation and treatment. If the subject is discharged before Day 7 then daily visits to the hospital should be performed up to Day 7. Further evaluations will be performed on Days 10 and 14.
2. Part 2 (Stabilisation Phase): Outpatient phase at which FEV1 will be collected at all visits up to Week 26 and/or early termination of the study.

A number of exploratory assessments will be performed throughout the study and will include an exploratory composite scale. The BODE index will be calculated on Day 14, using the standard criteria of body mass index (BMI), FEV1 (percentage of predicted), mMRC dyspnoea scale and exercise tolerance using the 6-minute walk test.

The exploratory composite scale evaluates treatment failure as defined by:

1. Worsening of symptoms warranting the addition of antibiotics
2. Worsening of symptoms warranting an increase in dose of oral corticosteroids or initiation of new oral corticosteroids
3. Worsening of symptoms requiring additional treatment of oral corticosteroids and/or antibiotics after completion of the initial regimen
4. Re-hospitalisation due to worsening of COPD and requiring additional treatment during the duration of the study due to exacerbations of respiratory symptoms
5. COPD-related death.

A total of 12 visits are planned for the two parts of the study.

All subjects will have routine safety monitoring throughout the study, including TEAEs, 12-lead electrocardiograms (ECGs), vital signs, quantitative sputum culture (if collected as part of routine clinical care), haematology (including eosinophil percentages), blood chemistry, and urinalysis laboratory assessments.

Subjects will also be followed up for time to next moderate/severe COPD exacerbation and number of moderate/severe COPD exacerbations as secondary objectives.

Accumulating safety data will be reviewed periodically by an independent, external data monitoring committee (DMC). Once subjects have completed study treatment, all new reports of exacerbation of COPD and events of hospitalisations due to new exacerbations of COPD will be evaluated by an external Independent Adjudication Committee (IAC).

Number of Subjects:

It is planned that approximately 320 subjects will be screened to randomise approximately 270 subjects. It is expected that approximately 255 subjects will complete the study and follow-up.

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Diagnosis and Main Criteria for Inclusion:

Inclusion:

1. Male and female adults aged ≥ 40 years
2. Written informed consent obtained prior to any study-related procedure
3. Presence of an active exacerbation of the ongoing COPD requiring hospitalisation for treatment:
   *"A sustained worsening of the patient's condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics **and** need for hospitalisation*"
4. Subjects with a diagnosis of COPD with spirometry performed outside an exacerbation within the last 12 months prior to the Screening Visit
5. Current smokers or ex-smokers with a smoking history of at least 10 pack-years (pack-years = [number of cigarettes per day x number of years/20])
6. A FEV1 < 65% of the predicted normal value
7. A **documented** history of at least one moderate or severe COPD exacerbation in the 12 months preceding the Screening Visit that required antibiotics and/or systemic corticosteroid (addition or increment on subject current use) as defined below:
   - *"A sustained worsening of the patient's condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics **or** need for hospitalisation"*
   - Also, documented visits to an emergency department due to COPD exacerbation are considered acceptable to fulfil this criterion.
8. Current regular treatment for COPD (categories C and D according to GOLD guidelines, updated 2015) for at least 2 months prior to the Screening Visit with either:
   - Inhaled corticosteroids/long-acting β_2-agonist combination, long-acting muscarinic antagonist without regular use of any short-acting bronchodilator (any short-acting bronchodilator allowed if used as needed [PRN]) or
   - Inhaled corticosteroids/long-acting β_2-agonist combination, without regular use of any short-acting bronchodilator (any short-acting bronchodilator allowed if used PRN) or
   - Inhaled corticosteroids/long-acting muscarinic antagonist combination, without regular use of any short-acting bronchodilator (any short-acting bronchodilator allowed if PRN) or
   - Inhaled long-acting β_2-agonist and inhaled long-acting muscarinic antagonist (with any PRN short acting bronchodilator) or
   - Subjects under monotherapy with long-acting muscarinic antagonist (with any PRN short acting bronchodilator)
9. Ideally subjects should be screened, randomised and dosed on the same day. Where information is not available, the Screening period can be extended to a maximum of 24 hours before Randomisation and dosing.

Exclusion:

1. Current diagnosis of asthma
2. Subjects who have already completed treatment for the current exacerbation of COPD
   - Subjects whose treatment for the current exacerbation (systemic corticosteroids or antibiotics) was initiated longer than 24 hours before Randomisation
3. Subjects who have been treated with or require use of the following medications:
   - A course of systemic steroids longer than 3 days for COPD exacerbation in the 4 weeks prior to the

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current exacerbation
- A course of antibiotics for COPD exacerbation longer than 7 days in the 4 weeks prior to the current exacerbation
- Phosphodiesterase type 3/4 (PDE3/PDE4) inhibitors
- Any p38 mitogen-activated protein kinase (p38) inhibitor treatment
- Use of antibiotics for a lower respiratory tract infection (e.g. pneumonia) in the 4 weeks prior to the current exacerbation (except for treatment of the current exacerbation, but not longer than 2 days)

4. Subjects currently requiring intensive care unit (ICU) and/or mechanical ventilation
5. Subjects treated with non-cardioselective β-blockers in the 10 days preceding the Screening Visit. Those subjects may enter the study after non-selective β-blockers withdrawal and/or cardioselective β-blockers intake for at least 10 days before Randomisation
6. Subjects treated with long-acting anti-histamines unless taken at stable regimen at least 2 months prior to Screening and to be maintained constant during the study, or if taken as PRN
7. Known respiratory disorders other than COPD which may impact the efficacy of the study drug according to the investigator's judgement. This can include but is not limited to α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease
8. Subjects who have had pulmonary lobectomy or lung volume reduction surgery or lung transplantation
9. Subjects who have had a live vaccination in the last 30 days prior to study start
10. Subjects who have a clinically significant cardiovascular condition (including, but not limited to, unstable ischemic heart disease, New York Heart Association (NYHA) Class III/IV, left ventricular failure, acute myocardial infarction); or the current exacerbation is due to a cardiovascular condition
11. An abnormal and clinically significant 12-lead ECG which may impact the safety of the subject according to the investigator's judgement at Screening or Baseline
12. Subjects whose 12-lead ECG shows QTcF > 450 msec at Screening and at Randomisation visits; ECG does not need to be repeated if Screening and Randomisation visit are on the same day
13. Current diagnosis of pneumonia (clinical or radiographic), pulmonary embolus or pneumothorax
14. History of hypersensitivity to anti-cholinergics, β_2-agonist, corticosteroids or any of the excipients contained in any of the formulations used in the study which may raise contra-indications or impact the efficacy of the study drug according to the investigator's clinical judgement
15. Clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease which may impact the efficacy or the safety of the study drug according to the investigator's clinical judgement
16. Subjects with liver enzyme alterations (serum alanine aminotransferase and/or aspartate aminotransferase > 2 x upper limit of normal [ULN], bilirubin > 1.5 ULN)
17. Impairment of renal function (defined as creatinine clearance (CrCL) < 60 mL/min (estimated by Cockcroft-Gault)
18. Concomitant/recent use of the CYP3A inhibitors or P-gp inhibitors including, but not limited to macrolide antibiotics, troleandomycin, erythromycin, clarithromycin, roxithromycin and chloramphenicol (with the exception of azithromycin, which is not prohibited), and the calcium channel blockers verapamil and diltiazem; consumption of grapefruit will also be excluded (Refer to Table 10-1)
19. Unstable concurrent disease: e.g. uncontrolled hyperthyroidism, uncontrolled diabetes mellitus or other endocrine disease; significant hepatic impairment; significant renal impairment; uncontrolled gastrointestinal disease (e.g. active peptic ulcer); uncontrolled neurological disease; uncontrolled haematological disease; uncontrolled auto-immune disorders or other which may impact the efficacy or the safety of the study drug according to the investigator's judgement

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20. History of alcohol abuse and/or substance/drug abuse within 12 months prior to the Screening Visit
21. Participation in another interventional clinical study where the investigational drug was received within < 5 x half-lives of the drug or 8 weeks (whichever is longer) (6 months in the case of a monoclonal antibody) prior to the Screening Visit. Participation in observational/non-interventional studies is allowed
22. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive urine test at Screening
23. Sexually active men unless they are using double barrier method for the period of dosing and for the 5 half-lives (8 days) afterwards
24. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study and for 8 days after treatment with investigational medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilisation (surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilisation (at least 6 months prior to Screening). For female subjects on the study, the vasectomised male partner must be the sole partner for that subject
    - Combination of the following:
        a) Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for 3 months before taking study treatment
        b) Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhoea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had a surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child-bearing potential. Sexually active men must use double barrier method while taking drug and for 5 half-lives (8 days) after completing investigational medication and should not father a child in this period. A condom is required to be used also by vasectomised men in order to prevent delivery of the drug via seminal fluid.

Permitted concomitant medications

1. Long-acting anti-histamines if taken at stable regimen at least 2 months prior to Screening or if taken PRN. For subjects not on stable, long-acting anti-histamines, short courses are allowed during the study period (≤ 7 days). Other anti-histamines are allowed during the study period for a short course (≤ 10 days) or if taken PRN
2. If required for respiratory symptoms or a COPD exacerbation:
    - Systemic corticosteroid (oral/IV/intramuscular)
    - Inhaled short acting β_2-agonists and/or short acting muscarinic antagonists or combination of both
    - Nebulised β_2-agonists, anti-cholinergics and/or steroids
    - Antibiotics
    - Oxygen.

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3. Mechanical ventilation at the investigator's discretion
   - Mechanical ventilation is exclusionary at Screening. However, if the subject requires mechanical ventilation during the course of the study, they should remain on the study until Week 26, even if further study drug cannot be administered or assessment carried out.
4. Short courses (≤10 days) of nasal corticosteroids (maximum two courses) are allowed
5. Current regular therapy for COPD as stated in inclusion criterion 8
6. Current regular theophylline.

Test Product, Dose and Mode of Administration:

[redacted]

Placebo, Dose and Duration of Administration:

[redacted]

Duration of Treatment:

[redacted]

Variables:

Efficacy:

1. FEV1, FVC and FEV1/FVC on Day 1 to Day 7 (daily), 10, 14, and at Weeks 8,12 and 26
2. FEV1, FVC and FEV1/FVC from the most recent test performed within the last 12 months outside an exacerbation
3. Time to improvement of 100 mL in FEV1
4. AUC of FEV1
5. Respiratory rate on Days 1 to 7 (daily), Days 10, 14, and at Weeks 8,12 and 26
6. EXACT-PRO score daily from Baseline up to the end of subject participation
7. AUC of EXACT-PRO
8. Number of COPD-related deaths from first dose intake up to the end of study participation (Week 26)
9. Number of moderate/severe COPD exacerbations over time among groups
10. Time to next moderate/severe COPD exacerbation (in days)
11. Number of uses of rescue therapy during the study
12. Time from hospitalisation until the subject is medically ready for discharge
13. Exploratory composite endpoints:
    - Number of events of worsening of symptoms warranting the addition of antibiotics
    - Number of events of worsening of symptoms warranting an increase of oral dose of corticosteroids or initiation of new oral corticosteroids
    - Number of events of worsening symptoms requiring additional treatment with oral corticosteroids

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and/or antibiotics after completion of the initial regimen
- Number of events of COPD exacerbations that required re-hospitalisation
- Number of COPD-related deaths.

14. CRQ scores at Baseline, Day 14 and at Weeks 8, 12 and 26
15. Cumulative oral/IV steroid dose Days 1 to 14, and from Day 14 to Week 26
16. Blood biomarkers (IL-6, TNF-α, fibrinogen, hs-CRP, and MPO)
17. BCT197 exposure on Days 1, 3, and 5
18. Body Mass Index at Baseline, Days 7, 14, and Weeks 8, 12 and 26
19. Dyspnoea (mMRC dyspnoea scale) at Baseline, Days 7, 14, and Weeks 8, 12 and 26
20. Six minute walk test and BMI at day 14 (for BODE index calculation).

Pharmacokinetics:

1. Sparse PK sampling in all subjects on any two of the 3 dosing occasions will be undertaken: one sample to be taken pre-dose, one sample taken 0-2 h post-dose, one sample taken 4-8 hours post-dose and one sample no earlier than 12 hours post-dose.

Pharmacodynamics: N/A

Pharmacogenetics: N/A

Safety:

1. TEAEs/SAEs (from first dose of study drug until study completion)
2. TEAEs of special interest (pneumonia)
3. TEAEs of special interest (liver enzymes [ALT, AST, bilirubin total and fractions], rash, acneiform dermatitis, cervical/vaginal inflammation, headache and pruritus)
4. Vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure)
5. QTc intervals at Baseline, from Day 1 to Day 7 (daily), Days 10 and 14
6. Laboratory data including sputum cultures and blood eosinophil percentages.

Study Endpoints:

Primary:

Change in FEV1 from Baseline (pre-dose) at Day 7.

Secondary:

1. Comparison of forced expiratory volume in 1 second (FEV1) on Days 3, 10, and 14
2. Normalisation evaluation of spirometry parameter (FEV1, FVC, and FEV1/FVC) response over time (performed daily from Days 1 to 7, 10, and 14, and Weeks 8, 12 and 26) compared with the most recent test performed within the last 12 months outside an exacerbation (pre-study FEV1 , FVC and FEV1/FVC value)
3. Time taken to improvement of 100 mL in FEV1 compared to Baseline versus placebo
4. Comparison of AUC of FEV1 over time among groups
5. Change in RR over time (performed daily from Days 1 to 7, 10 and 14) among groups
6. Change in RR on Days 3, 7, 10 and 14 among groups

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7. Time to improvement based on EXACT-PRO total score
8. Comparison of AUC of EXACT-PRO over time among groups
9. Number of COPD-related deaths during the study
10. Number of moderate/severe COPD-related exacerbations during the study
11. Time to next moderate/severe COPD exacerbation
12. Change from Baseline at each inter-visit period and over the entire period of the study in the average EXACT-PRO total score and domain scores
13. Number of times each subject required rescue therapy during the study
14. Time from hospitalisation until the subject is medically ready (COPD-related) for discharge
15. Nonlinear mixed effects pharmacokinetic/pharmacodynamics (PK/PD) models evaluating the relationship between BCT197 exposure and efficacy/safety endpoints.

Safety:

1. TEAEs/SAEs (from first dose of study drug until study completion)
2. Evaluation of the incidence of pneumonia from first dose of study drug until completion
3. TEAEs of special interest (liver enzymes [ALT, AST, bilirubin total and fractions], rash, acneiform dermatitis, cervical/vaginal inflammation, headache and pruritus)
4. Vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure) and laboratory parameters
5. QTc intervals and ECG findings (arrhythmias, conduction blocks, changes in ST segment) at Baseline, from Day 1 to Day 7, Days 10 and 14
6. Laboratory data including sputum cultures and blood eosinophil percentages.

Exploratory:

1. Exploratory composite scale comparing the following among the three groups at Weeks 8, 12 and 26:
   - Number of events of worsening symptoms warranting the addition of antibiotics
   - Number of events of worsening of symptoms warranting an increase of oral dose corticosteroids or initiation of new oral corticosteroids
   - Number of events of worsening of symptoms requiring additional treatment with oral corticosteroids and/or antibiotics after completion of the initial regimen
   - Number of events of COPD exacerbations that required re-hospitalisation
   - Number of COPD-related deaths.
2. Change in CRQ from Baseline at Day 14 and Weeks 8, 12 and 26 to evaluate recovery, comparing among the three groups over time
3. Cumulative oral/IV steroid dose from Day 1 to Day 14, and from Day 14 to Week 26
4. Change in inflammatory blood biomarkers (IL-6, TNF-α, fibrinogen, hs-CRP, and MPO) daily during Part 1 of the study, and at Weeks 8, 12 and 26
5. Relationship between BCT197 exposure and efficacy/safety endpoints
6. Change from Baseline in mMRC dyspnoea scale over time
7. BODE index among the three groups at Day 14.

Statistical Methods:
Sample Size and Power:

[redacted]

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[redacted]

Change of FEV1 from Baseline up to and including Day 7 will be assessed with a mixed-model repeated measures (MMRM) analysis, with treatment regimen as a factor and Baseline FEV1 as a covariate. The adjusted mean difference between regimens will be presented along with 95% confidence intervals for the Day 7 time-point.

Exploratory exposure-response (E-R):

Nonlinear mixed effects modelling will be undertaken to evaluate the relationship between BCT197 exposure and selected safety/efficacy endpoints.

Version and Date of the Protocol: Final 5.0, 08 November 2016

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6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADME	absorption, distribution, metabolism and excretion
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ATF-2	activating transcription factor-2
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the curve
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
BODE	Body mass index, airflow Obstruction, Dyspnoea and Exercise index
BUN	blood urea nitrogen
C/EBP	CCAAT/enhancer binding protein
CHMP	Committee for Medicinal Products for Human Use
C_{max}	maximal concentration of analyte in blood/plasma
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CrCL	creatinine clearance
CRQ	chronic respiratory questionnaire
CYP3A	cytochrome P450 subtype 3A
DMC	Data monitoring committee
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
ERS	European Respiratory Society
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ER	emergency room
E-R	exposure-response
EUDRACT	European Union Drug Regulatory Agency Clinical Trial
EXACT-PRO	The EXAcerbations of Chronic pulmonary disease Tool-Patient Reported Outcome
FDA	Food and Drug Administration
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
GCP	Good Clinical Practice

GOLD	Global initiative for chronic obstructive lung disease
HR	heart rate
hs-CRP	high-sensitivity C-reactive protein
IAC	Independent adjudication committee
IBD	inflammatory bowel disease
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IEC	Independent ethics committee
IL-6	interleukin-6
IL-8	interleukin-8
INR	international normalised ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	intention to treat
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
Ki	inhibitory constant
KIM-1	kidney injury molecule-1
LPS	lipopolysaccharides
MAPK	mitogen activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	millilitre
MMRM	mixed model repeated measures
mMRC	modified Medical Research Council
MPO	myeloperoxidase
MSAP	modelling and simulation plan
MSS	medical and safety services
NNT	number needed to treat
NYHA	New York Heart Association
p38	p38 mitogen-activated protein kinase
p53	p53 tumour suppressor protein
PoC	proof of concept
PD	pharmacodynamics
PDE4	phosphodiesterase type 4
PK	pharmacokinetics

PFT	pulmonary function test
PP	per protocol
PRN	as needed
PRO	patient reported outcome
QTc	corrected QT interval of the electrocardiogram
RA	rheumatoid arthritis
RR	respiratory rate
RUQ	right upper quadrant
SABA	short-acting β_2 agonist
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoC	standard of care
SOP	standard operating procedure
STAT-1	Signal Transducers and Activators of Transcription
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TNF-α	tumour necrosis factor-alpha
ULN	upper limit of normal
6MWT	6-minute walk test

7 INTRODUCTION

7.1 Background

Chronic obstructive pulmonary disease (COPD) is a progressive condition that is a major cause of poor health and death worldwide (GOLD Guidelines 2015) and contributes significantly to health care costs and comorbidity (Lopez et al 2006), (Chapman et al 2006). COPD is a chronic disease for which worldwide prevalence (currently estimated at 210 million) and mortality rate (2.74 million died in 2000) are still increasing. COPD is currently ranked as the fourth cause of death (GOLD Guidelines 2015) and is anticipated to become the third by 2020.

COPD exacerbations account for 50-75% of the cost of healthcare services in COPD (Mittmann et al 2008, Toy et al 2010). The impact of the exacerbations on patient's overall well-being is significant, and the symptoms and deterioration in lung function may persist for several weeks before recovering to Baseline values (Seemungal et al 2000). On average, COPD patients experience approximately 1-3 exacerbations per year, although this varies with the severity of underlying COPD (Seemungal et al 2009; Langsetmo et al 2008). A median duration of exacerbation of 13 (6 to 24) days has been reported in patients receiving SoC, and 9 (6 to 14) days in patients receiving long-term therapy with macrolide antibiotics in addition to SoC. Of these exacerbations, 37% (patients treated with long-term macrolides in addition to SoC) and 60% (patients treated with SoC) had not resolved within 10 days (Seemungal et al 2008). A recent retrospective observational database study showed a median duration of hospital stay due to moderate to severe COPD exacerbation of 9 to 10 days (Molinari et al 2015). Based on published literature, approximately 32% of exacerbations occur within 8 weeks of a preceding exacerbation event (Hurst 2009), and approximately 60% of patients are readmitted to the hospital within 12 months because of an exacerbation (Almagro et al 2006; Garcia-Aymerich et al 2003; Lau 2001), highlighting the need for more effective treatments.

Since frequent COPD exacerbations are known to promote disease progression (Donaldson 2002 et al; Rennard and Farmer 2004), there is a high unmet need for more effective treatment to reduce the number and severity of exacerbations as well as the length and number of hospitalisations.

There is an increasingly pressing need for the effective treatment of exacerbations with limited options available, i.e., bronchodilators, oxygen, antibiotics and oral steroids. Since the seminal trials performed around 15 years ago (Davies et al 1999) oral corticosteroid use has become widespread for this indication. Following oral corticosteroid treatment, hospital stay is shortened by only 1.22 days (mean stay around 9 days) with a number needed to treat (NNT) of 10 to prevent one treatment failure (i.e. a change in the original treatment) at 30 days. However, there is no improvement in overall mortality when using oral corticosteroids and a significant risk of an adverse event occurring (one per 5 people treated). In particular, patients who frequently exacerbate have worse long term outcomes compared with those who do not and any therapy which can modulate the natural history of an

exacerbation with particular reference to the complete recovery of baseline lung function could potentially provide a significant therapeutic advance.

New treatments are needed that reduce the severity of exacerbations and provide a more effective treatment compared to current rescue therapies, particularly intravenous (IV) and oral steroids.

Therefore, there is an unmet need for an appropriate compound targeting the treatment of acute exacerbations, with anti-inflammatory activity, low systemic side effects, and with the potential to significantly change the way COPD patients and their exacerbations are managed.

The Mereo BioPharma 1 Ltd compound, BCT197, is an inhibitor of the p38 mitogen-activated protein kinase (MAPK). BCT197 is a 5-amino-pyrazole representing one series in the chemically diverse class of p38 MAPK inhibitors. The p38 MAPK pathway is activated in a variety of inflammatory conditions and p38 MAPK inhibitors have been studied in a number of different diseases, including severe asthma, COPD, acute coronary syndrome and auto-immune diseases such as rheumatoid arthritis (RA), psoriasis and inflammatory bowel disease (IBD) (Kumar et al 2003, Lee and Dominguez 2005) but with limited success.

Inhibition of p38 MAPK has been shown to block release of inflammatory mediators both *in vitro* and *in vivo*. p38 MAPK regulates transcription through the phosphorylation of transcription factors involved in the inflammatory process such as ATF-2, p53, C/EBP-homologous protein, muscle-specific transcription factor-2 and STAT-1. Inhibition of p38 MAPK blocks TNF-α and IL-8 release by LPS-stimulated monocyte/macrophages, IL-6 release by bronchial epithelial cells in response to cigarette smoke and regulates a range of different neutrophil functions including adhesion, activation, chemotaxis and apoptosis. Moreover, increased phosphorylation of p38 has been demonstrated in the lungs of COPD patients (Renda et al 2008, Chin et al 2005). Therefore, a putative blockade of this pathway should result in attenuation of airway inflammation seen in acute exacerbations of COPD.

Thus far, BCT197 has been investigated in three healthy volunteer studies [CBCT197A2205], [CBCT197A2101] and [CBCT197A1101] and in a proof of concept study in COPD [CBCT197A2201] and another study of acute kidney injury in subjects undergoing elective cardiac surgery with cardiopulmonary bypass (CPB) [CBCT197A2202].

Two healthy volunteer studies were single ascending dose studies, with doses from [redacted] were conducted in Caucasians [CBCT197A2101] and in Japanese volunteers [CBCT197A1101]. One healthy volunteer study was a single oral dose study to investigate the pharmacokinetics (PK) of 75 mg of ^{14}C-labelled BCT197 [CBCT197A2205].

Single administration of BCT197 at doses up to [redacted][CBCT197A2101] was well tolerated and provided nearly complete suppression of blood TNF-α levels after *in vivo* LPS challenge, showing that BCT197 might have an inhibitory effect on p38 MAPK signalling. However, acneiform rash occurred in 21 of 32 subjects treated with BCT197 once daily over 14 days at doses of [redacted] and in 5 of 16 placebo-treated subjects. Two of 16 subjects receiving single administration of BCT197 also exhibited acneiform rash after LPS challenge, although no

acneiform rash occurred in healthy subjects receiving single administration of BCT197 alone. The time of onset of acneiform rash varied widely among subjects ranging from the 8th day of repeated administration of BCT197, to about 1 week after completion of the 14-day treatment with BCT197.

In the human ADME study A2205, metabolism was found to be the principal method of clearance. The human metabolite was the acid compound M14 (BHA784). Based on plasma Cmax and AUC, the systemic exposure to M14 was about 40% of that of BCT197. The concentration-time curves of radioactivity for BCT197 and M14 were parallel, showing similar half-lives. Low levels of M14 were also found in skin biopsies. M14 was excreted mainly in urine (28% of dose). M14 is not pharmacologically active, i.e. it does not inhibit p38 MAP kinase to a relevant extent.

The proof of concept (PoC) study [CBCT197A2201] was conducted in subjects with acute exacerbations of COPD. The effects of BCT197 on COPD subjects presenting with an acute exacerbation were evaluated in this double-blind, placebo-controlled proof of concept study. [redacted]reater improvements in lung function (forced expiratory volume in 1 second [FEV1]) compared with placebo and prednisone, 2 days after single and repeat doses were consistently observed in all 4 study parts. However, in three of the treatment regimens these effects were only sustained for 2 days after dosing. No noticeable differences in FEV1 changes from Baseline compared to control arms were seen 4 days after dosing, with the exception of the 75 mg repeat dose on Day 6 which led to a greater improvement in lung function than placebo, sustained until study Day 14. In the PoC [CBCT197A2201] study, no acneiform rashes were observed.

CBCT197A2202 was a two-part study of BCT197 in the treatment of acute kidney injury (AKI) following cardiopulmonary bypass surgery for either coronary artery bypass grafting or cardiac valve repair/replacement. This was a PoC study to determine if a single, pre-operative dose of BCT197 ameliorated the decrease in estimated glomerular filtration rate (eGFR) associated with cardiac surgery with CPB, measured at 48 hours after dosing. The two parts, A and B, conducted in parallel. Part A was an open label design in subjects with eGFR in the 30 to 60 mL/min/1.73 m^2 range, inclusive, who were scheduled for elective cardiac surgery with CPB. Subjects received a single oral dose of [redacted] of BCT197 2 hours ± 30 minutes prior to the estimated time of initial sternal incision while in the pre-operative holding area. The subject had serial PK blood draws up to Day 5. The end of study procedures were conducted when the subject was discharged or at Day 8 after dosing. Part B was a double-blind, randomised, placebo-controlled study in subjects with eGFR > 60 mL/min/1.73 m^2 who were scheduled for elective cardiac surgery with CPB. Subjects received a single oral dose of [redacted] of BCT197 or placebo 2 hours ± 30 minutes prior to the estimated time of initial sternal incision while in the pre-operative holding area. Biomarker assessments, including KIM-1 and eGFR, were used to assess efficacy.

A total of approximately 140 subjects were planned to be enrolled to participate in the study and randomised. A total of eight subjects were assessed in Part A, and approximately

132 subjects were expected to be assessed in Part B. As of 31 October 2013, 83 Part B subjects had been enrolled (42 on active treatment). Serious adverse events (SAEs) have been reported in 23 subjects up to 31 October 2013. None of the SAEs was suspected to be related to study medication by the investigator. There have been no suspected unexpected serious adverse reactions (SUSARs). There was one death due to respiratory failure, sepsis, and multi-organ failure.

A preplanned interim analysis of Part B was conducted in October 2013 which included 66 subjects who had completed Day 5. At that time the AKI rate was higher on BCT197 [6/31 (19%)] than on placebo [2/33 (6%)], whereby AKI was defined as 25% or more reduction in eGFR at 48 hours. The reported (expected) control rate of AKI is in the 10 to 20% range. None of the subjects required dialysis. Furthermore, the number of subjects reporting SAEs in the BCT197 group [12 (36%)] was higher than that on placebo [3 (9%)], but these were distributed over several types of SAEs that were also expected in the cardiopulmonary bypass population. None of the SAEs was related to a kidney disorder and none was suspected to be related to study medication. The BCT197 group had an average baseline weight 9.1 kg heavier than the placebo group, suggesting that there may have been some degree of unbalanced randomisation. Based on the IA data, the Data Monitoring Committee (DMC) recommended to put the study on hold for reasons of lack of efficacy and the higher rate of SAEs on BCT197. According to the DMC the data did not allow assessment for a possible nephrotoxicity.

Based on the data available thus far, it appears that a regimen longer than a single dose would be required to sustain the effect of BCT197. Subjects will receive one of two oral dosing regimens of BCT197 or matching oral placebo administered according to the dosing schedules shown in Table 7-1.

[redacted]

BCT197 is intended to be prescribed as a treatment added to standard of care (SoC) of acute exacerbations in COPD and is envisaged to be used for repeated administration. BCT197 is formulated as oral capsules. The two dose regimens proposed for this study are based on the efficacy, toxicology, pharmacokinetic and safety data available thus far. [redacted] The rationales for the dose regimens proposed are based on the PK exposure and are explained in the Section 7.2 below.

7.2 Rationale

This study will be conducted in compliance with the protocol and with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

This study will investigate the efficacy, safety and tolerability of two different dosing regimens of BCT197 added to SoC (systemic corticosteroids and/or antibiotics) versus placebo added to SoC in subjects with severe acute exacerbations of COPD. The proposed doses take into account trough levels based on previous PK modelling to ensure that the study drug remains at effective concentrations between doses.

The approach is to provide rapid attenuation of inflammatory responses which occur during a severe acute exacerbation, typically 3 to 5 days, and so multiple dosing will take place to ensure appropriate plasma levels are present to allow effective treatment of an exacerbation. As previously noted, acneiform rash occurred in a number of subjects treated once daily with BCT197 over a 14-day period at doses of 3 to 10 mg. On this basis there is a clear desire to ensure that prolonged continuous exposure to BCT197 is avoided. Overall, a dose-dependent reduction in TNF-α levels has been observed following doses ranging from [redacted] BCT197, although flattening of this effect to between 45 to 50% of placebo levels occurred between doses of [redacted] A number of PK simulations have been performed looking at both dosing intervals [redacted], as well as dose levels [redacted]. Based on predicted exposures of the various regimens, there is no perceived benefit in dosing beyond [redacted] for a typical exacerbation. However, in order to initiate suppression of the inflammatory response the [redacted] dose in both regimes is higher than the doses on [redacted]. The 'high' dosing regimen (regimen 1) is initiated at [redacted] which is the highest dose which can be safely administered based on toxicology margins whereas the 'low' dose regimen is initiated at a 40 mg dose which approximates to the mid-point in the TNF-α response curve. The doses in the two regimens have been designed to minimise overlap of PK exposure and to differentiate the doses to allow a better understanding of the exposure/clinical response relationship.

The K_i values for p38 alpha and p38 beta are 49 and 72 nM, respectively, with IC_{50} values of 37 nM and 106 nM, respectively. Based on the PK profiles the high dose regimen, dosing at [redacted] should maintain drug levels above 220 ng/mL out to approximately [redacted] This should achieve a plasma concentration of 5.7 µM. BCT197 has a very low first pass metabolism pre-clinically with the oral bioavailability estimated at 93% in the rat, 87% in the dog and 90% in the monkey. The *in vitro* data show that it is only weakly protein bound with free fraction in man (human plasma samples) ranging from 13 to 25%.

Using the most conservative estimate (13%), the concentration based on free fraction will be at or above 740 nM for the duration of the dosing interval. C_{max} would be around 2 µM based on the first dose. Estimated drug levels are approximately 7 to 10 times higher in concentration than the K_i and IC_{50} values and therefore >99% enzyme inhibition would be expected to occur for 6 days. Assuming a PK variability of 50%, drug levels would still be expected to be 3 to 5 times above the K_i and so would produce high levels of inhibition, potentially in the range of 90 to 99%.

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objective is to evaluate the efficacy of two different dosing regimens of BCT197 added to SoC versus placebo added to SoC in the treatment of acute respiratory exacerbations of COPD that required hospitalisation by comparison of change in FEV1 from Baseline (pre-dose) to Day 7.

8.2 Secondary Objectives

The secondary objectives are to evaluate the efficacy and tolerability of two different dosing regimens of BCT197 added to SoC versus placebo added to SoC in treatment of an acute exacerbation of COPD requiring hospitalisation by measuring the following:

1. Comparison of FEV1 on Days 3, 10, and 14
2. Normalisation evaluation of spirometry parameter (FEV1, forced vital capacity [FVC], and FEV1/FVC) response over time (performed daily from Days 1 to 7, 10, and 14, and Weeks 8, 12 and 26) compared with the most recent test performed within the last 12 months outside an exacerbation (pre-study FEV1, FVC, and FEV1/FVC value)
3. Time taken to improvement of 100 mL in FEV1 compared to Baseline versus placebo
4. Assessment of AUC of FEV1 over time among groups
5. Respiratory rate (RR) normalisation over time (performed daily from Days 1 to 7, 10 and 14) among groups
6. RR at Days 3, 7, 10, and 14 among groups
7. Time to improvement based on EXACT-PRO total score
8. Assessment of AUC of EXACT-PRO over time among groups
9. Evaluate the number of COPD-related deaths among groups
10. Evaluate the number of moderate/severe COPD exacerbations (classified according to European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) guidelines, refer to Section 11.2.3) over time among groups
11. Evaluate time to next moderate/severe COPD exacerbation
12. Change from Baseline at each inter-visit period and over the entire period of the study in the average EXACT-PRO total score and domain scores
13. Evaluate the use of rescue therapy during the study
14. Evaluate time from hospitalisation until subject is medically ready (COPD-related) for discharge
15. To characterise the PK of BCT197 in adults with COPD.

Safety and tolerability of BCT197

1. Evaluation of each treatment emergent adverse event (TEAE)/SAE (from first dose of study drug until study completion)
2. Evaluation of the incidence of pneumonia from first dose of study drug until study completion
3. TEAEs of special interest: rash, acneiform dermatitis, cervical/vaginal inflammation, headache, pruritus and liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin)
4. Evaluation of vital signs and laboratory parameters
5. Evaluation of QTc intervals over time at Baseline, Day 1 to Day 7 (daily), Days 10 and 14
6. Quantitative sputum culture over Days 1 to 14 whenever sputum is collected for clinical purposes.

8.3 Exploratory Objectives

Exploratory assessments will evaluate:

1. Exploratory composite scale endpoints comparing among the three groups at Weeks 8, 12 and 26
    - Number of events of worsening of symptoms warranting the addition of antibiotics
    - Number of events of worsening of symptoms warranting an increase of oral dose of corticosteroids or initiation of new oral corticosteroids
    - Number of events of worsening of symptoms requiring additional treatment with oral corticosteroids and/or antibiotics after completion of the initial regimen
    - Number of events of COPD exacerbations that required re-hospitalisation
    - Number of COPD-related deaths.
2. Chronic respiratory questionnaire (CRQ) at Baseline, Day 14 and at Weeks 8, 12 and 26 to evaluate recovery comparing among the three groups over time
3. Cumulative oral /IV steroid dose on Days 1 to 14, and from Day 14 to Week 26
4. Change in inflammatory blood biomarkers (IL-6, TNF-α, fibrinogen, high-sensitivity C-reactive protein [hs-CRP], and myeloperoxidase [MPO]) daily during Part 1 of the study, and at Weeks 8, 12 and 26
5. Explore the relationship between BCT197 exposure and efficacy/safety endpoints
6. Change from Baseline in modified Medical Research Council (mMRC) dyspnoea scale over time
7. Body mass index, airflow Obstruction, Dyspnoea and Exercise (BODE) index among the three groups at Day 14.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1.1 Description

This is a phase IIa, two-part, randomised, multi-centre, multinational, double-blind, placebo-controlled, parallel-group study of 26 weeks duration in adult subjects with acute respiratory exacerbations in COPD. It will be conducted in approximately 90 centres in approximately 12 countries. It is planned that approximately 320 subjects will be screened to enrol approximately 270 subjects, and expected that approximately 255 subjects will complete the study and follow-up. Only hospitalised subjects will be recruited.

Two regimens of BCT197 added to SoC (which includes at least steroids and/or antibiotics) will be compared with placebo added to SoC.

Subjects that agree to participate in the study (informed consent form [ICF] process completed; subject has signed and dated the ICF) will be assessed for eligibility by confirming inclusion/exclusion criteria.

After confirmation that all of the inclusion criteria and none of the exclusion criteria are met, the subject will be randomised on Day 1 in a 1:1:1 ratio to 1 of 2 BCT treatment schedules or placebo; all subjects will undergo SoC assessments regardless of treatment group. Randomisation will be via Interactive Response Technology (IRT) to ensure proper distribution among groups with respect to demographic data (age, gender), severity of disease, heart failure, oxygen saturation (without oxygen supplementation), and FEV1.

After Randomisation, Part 1 (Acute Exacerbation Phase) of the study continues with daily evaluation up to Day 7. Further evaluations will be performed on Days 10 and 14. Subjects will receive their first dose of study treatment within a maximum of 24 hours after presenting with an acute exacerbation (Day 1). Subjects will be eligible only if their treatment (SoC) has been initiated less than 24 hours before Randomisation and dosing. Study treatment will be administered on Days 1, 3 and 5. Subjects will undergo all safety and efficacy assessments on Day 1. Physical examinations, 12-lead ECGs, pulmonary function test (PFT; spirometry), and blood sampling for blood biomarkers will be done every day during the Acute Exacerbation Phase (Days 1 to 7, Day 10 and Day 14). It is expected that subjects will be hospitalised during Part 1 (Day 1 - Day 7). However, if a subject improves and is discharged prior to Day 7, the subject should return to the facility daily through to Day 7 and on Days 10 and 14 for completion of study assessments. Upon discharge the subject will be given a diary to document any occurrences of COPD and rescue medication use.

Part 2 (Stabilisation Phase) of the study requires subject evaluations at Weeks 8, 12 and 26. During Part 2 of the study, the subject's medical condition will be monitored at each visit and SoC medication adjusted as needed.

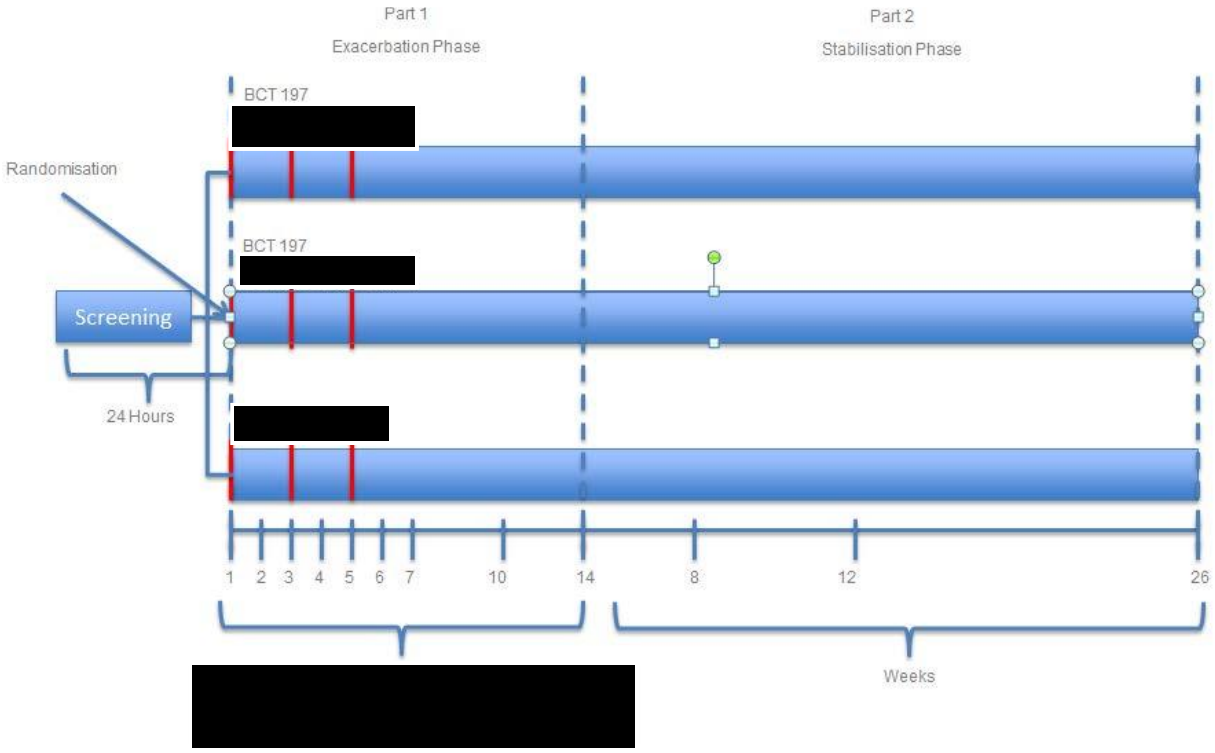
The End of Study is defined as the last visit of the last global subject.

Subjects will undergo sparse PK sampling (4 samples collected on any 2 of the 3 treatment days).

This study does not restrict the appropriate care of the subject and allows 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 GOLD (2015) for the treatment of acute exacerbations of COPD, subjects must be receiving at least steroids and/or antibiotics. However medications that may interfere with metabolism of the study drug or that may bring additional risk to the subject should be avoided. These medications are referred as prohibited concomitant medications (Table 10-1) and are exclusionary from the study.

A study schematic is provided in (Figure 9-1).

Figure 9-1: Schematic of Study Design



9.1.2 Schedule of Assessments

The schedule of assessments is presented in Table 9-1.

Table 9-1 Schedule of Assessments

	Acute Exacerbation Phase									Stabilisation phase		
Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
	Screening[1]	**Randomisation/ Baseline[1] Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Week 8 (± 3 days)**	**Week 12 (± 3 days)**	**Week 26 (± 3 days)**
Written Informed consent	X												
Demographics	X												
Medical history including current medical conditions[17]	X												
Smoking history	X												
Inclusion/exclusion criteria	X												
Full physical examination[2, 15]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[3,4,7]	X	X	X	X	X	X	X	X	X	X			
Assessment of inflammation of cervix and vagina[16]	X							X		X			
Pregnancy test[4]	X										X	X	X
Clinical laboratory tests[2,5,6] (haematology, blood chemistry and urinalysis laboratory assessments)	X	X		X		X		X	X	X	X	X	X
PK assessment[7]		X		X		X							
PFT (Spirometry)	X[9,13]	X[8,13]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8,14]	X[8,14]	X[8,14]
Randomisation		X											
mMRC,		X						X		X	X	X	X

6MWT/BMI[10]									X			
CRQ		X							X	X	X	X
Blood biomarkers[6,11]		X	X	X	X	X	X	X	X	X	X	X	X
Exploratory composite scale									X	X	X	X
EXACT-PRO		X	X	X	X	X	X	X	X	X	X	X	X
Study treatment		[redacted]											
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Ideally subjects should be screened and randomised and dosed on the same day. There will be no separate Screening Visit as subjects will receive their first dose of study treatment within 24 hours of presenting with an acute exacerbation. Subjects will be eligible only if their treatment (SoC) has been initiated less than 24 hours before Randomisation and dosing (Day 1). For screen failures, re-screening may be performed 1 month after complete recovery from a previous acute exacerbation of COPD.

2 Vital signs and laboratory assessments should where feasible be performed before salbutamol intake. Height is to be measured at Screening only. Vital signs include body temperature, RR, pulse rate, blood oxygen (measured using a pulse oximeter), systolic and diastolic blood pressure. If Screening and Day 1 are on the same day and there is no medical indication, then vital signs and physical examination noted for Visit 1 do not need to be repeated. If Visit 1 is performed over different days, vital signs and physical examination should be repeated on Day 1 prior to randomisation only if the subject's condition has deteriorated.

3 12-lead ECG will be performed after 10 minutes rest. If the Screening Visit and Day 1 are on the same day and there is no medical indication then the ECG noted for Visit 1 does not need to be repeated. If Visit 1 is performed over different days, the ECG should be repeated on Day 1 prior to randomisation.

4 For women of child-bearing potential only. Urine dipstick pregnancy tests carried out by site at Screening and at all indicated visits; serum pregnancy tests will be performed centrally at the Screening and last visit only. Urine pregnancy tests will be used for the purposes of inclusion into the study due to the acute nature of the study.

5 Prior to entry into the study (Visit 1), clinical laboratory tests will be performed at a local laboratory to confirm eligibility for randomisation. These tests will also be performed by the central laboratory. If Screening and Day 1 are on the same day and there is no medical indication, then the clinical laboratory tests noted for Visit 1 do not need to be repeated. If Visit 1 is performed over different days, the local laboratory should repeat clinical laboratory tests on Day 1 if the subject's condition has deteriorated.

6 All blood samples are to be collected at least 6 hours after SABA intake whenever possible (times of sample collection and SABA intake must be recorded), 8 hours fasting (where possible) and after ECG and vital signs (including RR). INR and prothrombin time not required during the Stabilisation phase.

7 There will be sparse PK sampling in all subjects to be taken on any 2 of the 3 dosing occasions (Days 1, 3, or 5): one sample to be taken pre-dose, one sample taken 0-2 h post-dose, one sample taken 4-8 hours post-dose, and one sample no earlier than 12 hours post-dose. ECG will be taken at approximately the same time as with PK sample. ECGs should be taken before the PK sample.

8 Spirometry will be taken 'on bronchodilator' and ideally in the morning. For an individual spirometry should be taken at approximately the same time of day (during the acute phase ± 1 hour and in the stabilisation phase ± 2 hour window). Ideally this will be taken at least 1 hour after regular long acting bronchodilators and 30 minutes after short acting bronchodilator medication. Time of last short and long acting bronchodilators will be documented.

9 Spirometry at Screening should be performed 'on bronchodilator'. This will be taken after any regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication.

10 Perform BMI and 6MWT at Day 14. BODE will then be calculated.

11 Please refer to the Laboratory Manual for clarification of whether the biomarker is to be analysed in either serum or plasma.

12 If the subject is discharged before Day 7, they will return to the hospital daily for assessment.

13 If screening and Day 1 occur on different days spirometry will be repeated on day 1 before dosing with study treatment and result obtained on day 1 may be used as baseline.

14 If historical spirometry data within last 12 months does not include pre and post SABA value this should be obtained during the stabilisation phase, for demographic purposes.

15 Physical examination at screening should include a minimum of chest, cardiovascular and abdominal examination. At all other time points a minimum of chest auscultation is required. Additional examination is at the discretion of the Investigator as indicated by the subjects' clinical condition.

16 A gynaecological history should be taken (from females only) with subjects specifically asked about vaginal bleeding, discharge or pain. Any new vaginal bleeding (other than normal menstruation), vaginal discharge or pain after dosing should be investigated by vaginal examination and any required specialist assessment.

17 Document in eCRF which symptoms of the acute exacerbation are present out of increased sputum, increased cough and increased dyspnoea.

Abbreviations: BMI = body mass index; BODE = Body mass index, airflow Obstruction, Dyspnoea and Exercise index; COPD: chronic obstructive pulmonary disease; CRQ = chronic respiratory questionnaire; ECG = electrocardiogram; eCRF: electronic case report form; EXACT-PRO: The EXAcerbations of Chronic pulmonary disease Tool-Patient Reported Outcome; INR: international normalised ratio; mMRC = modified Medical Research Council; PFT = pulmonary function test; PK = pharmacokinetics; RR = respiratory rate; SABA = short-acting β_2 agonist; SoC: standard of care; 6MWT = 6-minute walking test

9.1.3 Study Assessments

9.1.3.1 Screening (Visit 1)

Subjects will be screened on the day that they present with an acute exacerbation (Day 1); there will be no separate Screening Visit as subjects will receive their first dose of study treatment within 24 hours of presenting with an acute exacerbation. Subjects will be eligible only if their treatment (SoC) has been initiated less than 24 hours before Randomisation and dosing (Day 1). For screen failures, re-screening may take place 1 month after complete recovery from a previous acute exacerbation of COPD.

The following procedures/assessments will be done:

1. Collection of the written informed consent signed by the subject, after the study has been fully explained by the investigator. The investigator or his/her designee should provide enough time and opportunity to inquire about details of the study and to decide whether or not to participate in the study, however respecting the study timelines defined in the inclusion and exclusion criteria
2. Collection of demographic data and medical/surgical/psychiatric history, including smoking history and gynaecological history (females)
3. Exacerbation assessment to verify a documented history of at least one exacerbation in the 12 months preceding Screening
4. Verification that spirometry has been performed within the last 12 months and outside of an exacerbation
5. Physical examination, including vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure), height, and weight
6. 12-lead electrocardiogram (ECG); recorded after 10 minutes at rest
7. Urine and serum pregnancy test, women of child-bearing potential only
8. Blood sample for clinical laboratory tests (haematology and biochemistry) to be taken at least 6 hours after SABA (whenever possible; times of sample collection and SABA intake must be recorded), after 8 hours of fasting (whenever possible), and after completion of ECG and vital signs (body temperature, RR, pulse rate, systolic and diastolic blood pressure). These clinical laboratory tests will performed both at the local and central laboratory to confirm eligibility for Randomisation
9. Urinalysis (specific gravity, pH, protein, glucose, blood)
10. 'On bronchodilator' spirometry. This will be taken after regular long acting bronchodilators and 30 minutes after short acting bronchodilator
11. Confirm inclusion and exclusion criteria
12. Document in eCRF which of the following three symptoms of the acute exacerbation are present

- Increased sputum
- Increased cough
- Increased dyspnoea.

Adverse events (AEs) and concomitant medications will be documented from the time the subject has signed the ICF.

9.1.3.2 Day 1 to Day 14 – Acute Exacerbation Phase

All subjects will initially be hospitalised. However, if a subject improves and is discharged prior to Day 7, the subject should return to the study facility daily up to and including Day 7 for study drug administration and completion of study assessments.

The subject should receive a diary on Day 1 after Randomisation and be instructed in its use. Prior to hospital discharge, the subject should be reminded about the use of the diary and need to bring their diary to all visits.

Study Day 1, Visit 1 (prior to study drug administration)

Once Screening has been completed, the following assessments/procedures will be done for all subjects:

1. Concomitant medication
2. If the Screening visit and Day 1 are performed on different days, the following assessments should be repeated at Day 1 prior to Randomisation only if the subject's condition has deteriorated:
    - Physical examination, including vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure) and weight
    - Blood sample for clinical laboratory tests (haematology and biochemistry) to be taken at least 6 hours after SABA (whenever possible; times of sample collection and SABA intake must be recorded), after 8 hours of fasting (wherever possible), and after completion of ECG and vital signs (body temperature, RR, pulse rate, systolic and diastolic blood pressure). These clinical laboratory tests will be performed at both the local and central laboratory to confirm eligibility for Randomisation
    - Urinalysis (specific gravity, pH, protein, glucose, blood)
3. 12-lead ECG; recorded after 10 minutes at rest
4. Randomisation via IRT to allocate subjects to a treatment group. All necessary data for completing the IRT system, per IRT manual, should be available
5. Chronic respiratory questionnaire (CRQ); Visit 1 questionnaire will be considered the Baseline score
6. Collection of mMRC dyspnoea scale

7. Blood sample for clinical laboratory tests (inflammatory blood biomarkers) to be taken at least 6 hours after SABA (whenever possible; times of sample collection and SABA intake must be recorded), after 8 hours of fasting (not essential if this is the initial visit), and after completion of ECG and vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure)
8. PK assessment (There will be sparse PK sampling in all subjects, to be taken on any 2 of the 3 [redacted]): one sample to be taken pre-dose, one sample taken 0-2 hours post-dose, one sample taken 4-8 hours post-dose, and one sample no earlier than 12 hours post-do[redacted]
9. 12 lead ECG to be performed at the same time as PK sample (ECG should be conducted before the blood sample is taken)
10. Delivery of diary and training for use
11. EXACT-PRO completed by the subject in the evening; the Visit 1 questionnaire will be considered the Baseline score
12. Spirometry. If Day 1 and screening occur on different days spirometry will be done on Day 1 (and may be used as the baseline value). This should be done ideally in the morning, at least 1 hour after regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication.

Study Day 1 (study drug administration)

[redacted]

2. Adverse event monitoring.

Study Days 2, 4 and 6

The following assessments will be done for all subjects, regardless of treatment group:

1. Adverse event monitoring
2. Concomitant medication
3. Physical examination, including vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure) and weight
4. 12-lead ECG; recorded after 10 minutes at rest
5. Blood sample for clinical laboratory tests (inflammatory blood biomarkers) to be taken at least 6 hours after SABA (whenever possible; times of sample collection and SABA intake must be recorded), after 8 hours of fasting (wherever possible), and after completion of ECG and vital signs (body temperature, RR, pulse rate, systolic and diastolic blood pressure)

6. If sputum or bronchoalveolar culture is collected for any medical reason (qualitative or quantitative culture) the result should be recorded in the electronic case report form (eCRF)
7. 'On bronchodilator' spirometry. Spirometry will ideally be performed in the morning, at least 1 hour after regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication
8. COPD exacerbation reporting (EXACT-PRO) completed by the subject in the evening in the Diary.

Study Days 3 and 5

The following assessments will be done for all subjects, regardless of treatment group:

1. Adverse event monitoring
2. Concomitant medication
3. Physical examination, including vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure) and weight
4. 12-lead ECG; recorded after 10 minutes at rest before dose with study treatment and at the same time as PK sample (ECG will be done before the blood sample)
5. Blood sample for clinical laboratory tests (haematology, biochemistry, and inflammatory blood biomarkers) to be taken at least 6 hours after SABA (whenever possible; times of sample collection and SABA intake must be recorded), after 8 hours of fasting (wherever possible), and after completion of ECG and vital signs (body temperature, RR, pulse rate, systolic and diastolic blood pressure)
6. Urinalysis (specific gravity, pH, protein, glucose, blood)
7. PK assessment (There will be sparse PK sampling in all subjects, to be taken on any 2 of the 3 dosing occasions (Days 1, 3, or 5): one sample to be taken pre-dose, one sample taken 0-2 hours post-dose, one sample taken 4-8 hours post-dose, and one sample no earlier than 12 hours post-dose)
8. If sputum or bronchoalveolar culture is collected for any medical reason (qualitative or quantitative culture), the result should be recorded in the eCRF
9. 'On bronchodilator' spirometry. This will ideally be performed in the morning, at least 1 hour after regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication

1[redacted]

11. COPD exacerbation reporting (EXACT-PRO) completed by the subject in the evening.

Study Day 7

The following assessments will be done for all subjects, regardless of treatment group:

1. Adverse event monitoring
2. Concomitant medication
3. Physical examination, including vital signs (body temperature, blood oxygen [measured using a pulse oximeter], RR, pulse rate, systolic and diastolic blood pressure) and weight
4. Gynaecological symptoms questions (change in bleeding (other than normal menstruation), discharge or pain. Any new symptoms should be followed up with a vaginal examination and specialist assessment as indicated (Females only)
5. 12-lead ECG; recorded after 10 minutes at rest
6. Blood sample for clinical laboratory tests (haematology, biochemistry, and inflammatory blood biomarkers) to be taken at least 6 hours after SABA (whenever possible; times of sample collection and SABA intake must be recorded), after 8 hours of fasting (wherever possible), and after completion of ECG and vital signs (oral body temperature, RR, pulse rate, systolic and diastolic blood pressure)
7. Urinalysis (specific gravity, pH, protein, glucose, blood)
8. If sputum or bronchoalveolar culture is collected for any medical reason (qualitative or quantitative culture), the result should be recorded in the eCRF
9. 'On bronchodilator' spirometry. This will ideally be performed in the morning, at least 1 hour after regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication
10. Collect mMRC dyspnoea scale
11. COPD exacerbation reporting (EXACT-PRO) completed by the subject in the evening.

Study Day 10

1. Adverse event monitoring
2. Concomitant medication
3. Physical examination, including vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure) and weight
4. 12-lead ECG; recorded after 10 minutes at rest
5. Blood sample for clinical laboratory tests (haematology, biochemistry, and inflammatory blood biomarkers) to be taken at least 6 hours after SABA (whenever possible; times of sample collection and SABA intake must be recorded), after 8 hours of fasting (wherever possible), and after completion of ECG and vital signs (body temperature, RR, pulse rate, systolic and diastolic blood pressure)

6. Urinalysis (specific gravity, pH, protein, glucose, blood)
7. If sputum or bronchoalveolar culture is collected for any medical reason (qualitative or quantitative culture), the result should be recorded in the eCRF
8. 'On bronchodilator' spirometry. This will ideally be performed in the morning, at least 1 hour after regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication
9. COPD exacerbation reporting (EXACT-PRO) completed by the subject in the evening.

Study Day 14

1. Adverse event monitoring
2. Concomitant medication
3. CRQ
4. Collect data for the exploratory composite scale
5. Physical examination, including vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure) and weight
6. Gynaecological symptoms questions (new bleeding except normal menstruation, discharge, pain). Any new symptoms should be assessed by vaginal examination and specialist assessment as indicated (females only)
7. 12-lead ECG; recorded after 10 minutes at rest
8. Blood sample for clinical laboratory tests (haematology, biochemistry, and inflammatory blood biomarkers) to be taken at least 6 hours after SABA (whenever possible; times of sample collection and SABA intake must be recorded), after 8 hours of fasting (wherever possible), and after completion of ECG and vital signs (body temperature, RR, pulse rate, systolic and diastolic blood pressure)
9. Urinalysis (specific gravity, pH, protein, glucose, blood)
10. If sputum or bronchoalveolar culture is collected for any medical reason (qualitative or quantitative culture), the result should be recorded in the eCRF
11. 'On bronchodilator' spirometry. This will ideally be performed in the morning, at least 1 hour after regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication
12. Collect mMRC dyspnoea scale
13. Perform the 6 minute walk test (6MWT) and BMI (for calculation of the BODE)
14. COPD exacerbation reporting (EXACT-PRO) completed by the subject in the evening.

9.1.3.3 Weeks 8, 12 and 26 – Stabilisation Phase

Subjects will return to the facility for 3 follow-up visits, at which time the following assessments/procedures will be done:

1. Adverse event monitoring
2. Concomitant medication
3. CRQ
4. Collect data for the exploratory composite scale
5. Physical examination, including vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure) and weight
6. Urine and serum (Week 26 only) pregnancy test, women of childbearing potential only
7. Blood sample for clinical laboratory tests (haematology [INR and prothrombin time not required], biochemistry, and inflammatory blood biomarkers) to be taken at least 6 hours after SABA (whenever possible; times of sample collection and SABA intake must be recorded), after 8 hours of fasting (wherever possible), and after completion of ECG and vital signs (body temperature, RR, pulse rate, systolic and diastolic blood pressure)
8. Urinalysis (specific gravity, pH, protein, glucose, blood)
9. If sputum or bronchoalveolar culture is collected for any medical reason (qualitative or quantitative culture), the result should be recorded in the eCRF
10. 'On bronchodilator' spirometry. This will ideally be performed in the morning, at least 1 hour after regular long acting bronchodilator administration and 30 minutes after short acting bronchodilator medication
11. Collect mMRC dyspnoea scale
12. COPD exacerbation reporting (EXACT-PRO) completed by the subject in the evening
13. Pre and post bronchodilator spirometry (week 8, 12 or 26). Where this is not available from historical spirometry this will be collected during the stabilisation period, for demographic purposes.

9.2 Discussion of Study Design

There are two components to a COPD exacerbation; one is related to the cause of the exacerbation and the other to the intensity of the inflammatory response of the airways and lungs. This inflammatory response of the airways results in local oedema and increased constriction of airway muscle, leading to an increased airway resistance to airflow, worsening dyspnoea, and fatiguing respiratory musculature. The natural course of COPD exacerbation indicates that inflammation is most intense at the initial stages. Anti-inflammatory treatment with steroids for as little as three days has been shown to improve FEV1 (Albert et al, 1980), and a recent trial (Leuppi et al, 2013) suggests that a 5-day treatment course is as effective as

the current practice of continuing anti-inflammatory therapy for two weeks or longer (Niewoehner et al, 1999).

The aim of treatment with BCT197 is to reduce the intensity of the inflammatory response and its effect on airways, thus increasing the rate of recovery of pulmonary function without the side effects associated with corticosteroids. The intention is to minimise the complications associated with COPD exacerbations, reduce the requirement for ventilator support, decrease the incidence of relapses over time, and restore previous functional status more quickly.

The objectives of this study are to prove the concept that the addition of BCT197 to SoC for COPD exacerbation improves subject recovery at two different regimen doses. As a secondary objective, two different dosing regimens of BCT197 added to SoC will be evaluated to compare efficacy and tolerability versus placebo added to SoC on pulmonary function recovery, stabilisation of airways and impact on subject well-being. FEV1 will be the primary variable as they reflect airway inflammation and respiratory effort. The study is designed in 2 parts. The first part is the Acute Exacerbation Phase, during which the subject will be evaluated daily for 7 days, then at Days 10 and 14. The second part is the Stabilisation Phase, designed to detect recurrences of exacerbations and to measure recovery of the subject to previous respiratory status and subject well-being.

9.2.1 Risk/Benefit and Ethical Assessment

The study explores the effect of BCT197 as add-on therapy to current therapies versus placebo added to SoC, thus all enrolled subjects will continue to receive standard of care for their severe acute exacerbation of COPD, including systemic corticosteroids and/or antibiotics, as defined by GOLD updated version 2015.

BCT197 thus far has been investigated in two healthy volunteer studies, as well as in a PoC study in COPD [CBCT197A2201] and in another PoC study in acute kidney injury (AKI) [CBCT197A2202]. Rash, gastrointestinal (GI) toxicity, hepatotoxicity, headache and dizziness are some of the class effects of p38 MAPK inhibitors.

In the multiple dose-ascending study [CBCT197A2101] the percentage of rash has been proportionately high in healthy volunteers treated with both placebo and BCT197 doses of [redacted].

In the CBCT197A2201 study in acute exacerbation COPD subjects, no acneiform rashes were observed.

The benefit/risk assessment of using BCT197 to treat COPD exacerbations is positive if BCT197 proves to be efficacious. COPD exacerbations can be life threatening, whereas the occurrence of a rash which is mild and transient in nature, is not serious compared with the COPD exacerbation. The risk to subjects in this study will be minimised by compliance with the inclusion/exclusion criteria, close clinical monitoring, including signs and symptoms related to the potential risks of p38 MAPK 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 will be performed throughout the study.

9.3 Selection of Study Population

9.3.1 Inclusion criteria

1. Male and female adults aged ≥ 40 years
2. Written informed consent obtained prior to any study-related procedure
3. Presence of an active exacerbation of the ongoing COPD requiring hospitalisation for treatment:

   *"A sustained worsening of the patient's condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics **and** need for hospitalisation".*
4. Subjects with a diagnosis of COPD with spirometry performed outside an exacerbation within the last12 months prior to the Screening Visit
5. Current smokers or ex-smokers with a smoking history of at least 10 pack years (pack-years = [number of cigarettes per day x number of years/20])
6. A FEV1 < 65% of the predicted normal value
7. A **documented** history of at least one moderate or severe COPD exacerbation in the 12 months preceding the Screening Visit that required antibiotics and/or systemic corticosteroid (addition or increment on subject current use) as defined below:
   - *"A sustained worsening of the patient's condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics **or** need for hospitalisation"*
   - Also, documented visits to an emergency department due to COPD exacerbation are considered acceptable to fulfil this criterion.
8. Current regular treatment for COPD (categories C and D according to GOLD guidelines, updated 2015) for at least 2 months prior to the Screening Visit with either:
   - Inhaled corticosteroids/long-acting β_2-agonist combination, long-acting muscarinic antagonist without regular use of any short-acting bronchodilator (any short-acting bronchodilator allowed if used as needed [PRN]) or
   - Inhaled corticosteroids/long-acting β_2-agonist combination, without regular use of any short-acting bronchodilator (any short-acting bronchodilator allowed if used PRN or
   - Inhaled corticosteroids/long-acting muscarinic antagonist combination, without regular use of any short-acting bronchodilator (any short-acting bronchodilator allowed if PRN) or

- Inhaled long-acting β_2-agonist and inhaled long-acting muscarinic antagonist (with any PRN short acting bronchodilator) or
- Subjects under monotherapy with long-acting muscarinic antagonist (with any PRN short acting bronchodilator).

9. Ideally, subjects should be screened, randomised and dosed on the same day. Where information is not available, the Screening period can be extended to a maximum of 24 hours before Randomisation and dosing.

9.3.2 Exclusion Criteria

1. Current diagnosis of asthma
2. Subjects who have already completed treatment for the current exacerbation of COPD
   - Subjects whose treatment for the current exacerbation (systemic corticosteroids or antibiotics) was initiated longer than 24 hours before Randomisation.
3. Subjects who have been treated with or require use of the following medications (Refer to Table 10-1):
   - A course of systemic steroids longer than 3 days for COPD exacerbation in the 4 weeks prior to the current exacerbation
   - A course of antibiotics for COPD exacerbation longer than 7 days in the 4 weeks prior to the current exacerbation
   - Phosphodiesterase type 3/4 (PDE3/4) inhibitors
   - Any p38 MAPK p38 inhibitor treatment)
   - Use of antibiotics for a lower respiratory tract infection (e.g. pneumonia) in the 4 weeks prior to the current exacerbation (except for treatment of the current exacerbation, but not longer than 2 days).
4. Subjects currently requiring intensive care unit (ICU) and/or mechanical ventilation
5. Subjects treated with non-cardioselective β-blockers in the 10 days preceding the Screening Visit. Those subjects may enter the study after non-selective β-blockers withdrawal and/or cardioselective β-blockers intake for at least 10 days before Randomisation
6. Subjects treated with long-acting anti-histamines unless taken at stable regimen at least 2 months prior to Screening and to be maintained constant during the study, or if taken as PRN
7. Known respiratory disorders other than COPD which may impact the efficacy of the study drug according to the investigator's judgement. This can include but is not limited to α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease
8. Subjects who have had pulmonary lobectomy or lung volume reduction surgery or lung transplantation

9. Subjects who have had a live vaccination in the last 30 days prior to study start
10. Subjects who have a clinically significant cardiovascular condition (including, but not limited to, unstable ischemic heart disease, New York Heart Association (NYHA) Class III/IV, left ventricular failure, acute myocardial infarction); or the current exacerbation is due to a cardiovascular condition
11. An abnormal and clinically significant 12-lead ECG which may impact the safety of the subject according to the investigator's judgement at Screening or Baseline
12. Subjects whose 12-lead ECG shows QTcF > 450 msec at Screening and at Randomisation visits; ECG does not need to be repeated if Screening and Randomisation visit are on the same day
13. Current diagnosis of pneumonia (clinical or radiographic), pulmonary embolus or pneumothorax
14. History of hypersensitivity to anti-cholinergics, β_2-agonist, corticosteroids or any of the excipients contained in any of the formulations used in the study which may raise contra-indications or impact the efficacy of the study drug according to the investigator's clinical judgement
15. Clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease which may impact the efficacy or the safety of the study drug according to the investigator's clinical judgement
16. Subjects with liver enzyme alterations (serum alanine aminotransferase and/or aspartate aminotransferase > 2 x upper limit of normal [ULN], bilirubin > 1.5 ULN)
17. Impairment of renal function (defined as creatinine clearance [CrCL] < 60 mL/min [estimated by Cockcroft-Gault])
18. Concomitant/recent use of the CYP3A inhibitors or P-gp inhibitors including, but not limited to macrolide antibiotics troleandomycin, erythromycin, clarithromycin, roxithromycin and chloramphenicol (with the exception of azithromycin, which is not prohibited), and of the calcium channel blockers verapamil and diltiazem; consumption of grapefruit will also be excluded (Refer to Table 10-1)
19. Unstable concurrent disease: e.g. uncontrolled hyperthyroidism, uncontrolled diabetes mellitus or other endocrine disease; significant hepatic impairment; significant renal impairment; uncontrolled gastrointestinal disease (e.g. active peptic ulcer); uncontrolled neurological disease; uncontrolled haematological disease; uncontrolled auto-immune disorders, or other which may impact the efficacy or the safety of the study drug according to the investigator's judgement
20. History of alcohol abuse and/or substance/drug abuse within 12 months prior to the Screening Visit
21. Participation in another interventional clinical study where the investigational drug was received within < 5 x half-lives of the drug or 8 weeks (whichever is longer) (6 months in

the case of a monoclonal antibody) prior to the Screening Visit. Participation in observational/non-interventional studies is allowed

22. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive urine test at Screening

23. Sexually active men unless they are using double barrier method for the period of dosing and the 5 half-lives (8 days) afterwards

24. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study and for 8 days after treatment with investigational medication. Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilisation (surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilisation (at least 6 months prior to Screening). For female subjects on the study, the vasectomised male partner must be the sole partner for that subject
    - Combination of the following:
        a) Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for 3 months before taking study treatment.
        b) Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    - Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhoea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had a surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child-bearing potential. Sexually active men must use double barrier method while taking drug and for 5 half-lives (8 days) after completing investigational medication and should not father a child in this period. A condom is required to be used also by vasectomised men in order to prevent delivery of the drug via seminal fluid.

9.3.3 Withdrawal of Subjects from the Study

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs when a subject does not want to participate in the study anymore and does not want to attend any further visits or assessments, have further study related contact, or allow analysis of already obtained biologic material.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Investigational treatment must be discontinued and no further assessments conducted. All biological material that has not been analysed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communication or follow-up.

The investigator should discontinue participation of a given subject if, on balance, he/she believes that continuation would be detrimental to the subject's well-being. However the subject should be followed up to the end of the study and all study procedures should be performed per protocol. As a minimum, all assessments for Week 26 should be performed according to the Schedule of Assessments Table 9-1.

9.3.4 Study Drug Discontinuation

Subjects may voluntarily discontinue investigational treatment for any reason at any time. Subject decision on discontinuation of study drug does not imply an automatic withdrawal from the study. If the subject does not want to take study drug but desires to continue in the study he/she may remain in the study and continue to undergo all assessments/procedures.

Investigational treatment must be discontinued under the following circumstances:

1. Emergence of the following adverse events:
    - Absolute QTcF > 500 msec
    - Occurrence of class effects i.e., rash Grade 4 as defined by exfoliations and ulcerations (Galimont-Collen et al 2007)
2. Any of the following laboratory abnormalities:
    - Renal function values that require discontinuation:
        - Discontinue investigational treatment for a subject if individual serum creatinine increases ≥ 50% compared to Baseline (and is considered clinically significant), or in the event of treatment emergent proteinuria (albumin:creatinine ratio (ACR) > 300 mg/g or >30 mg/mmol; protein creatinine ration (PCR) ≥ 500 mg/g or >50 mg/mmol), unless the event is not drug related, or if the benefit/risk assessment supports continuing investigational treatment
        - A renal event leading to subject discontinuation should be followed up until event resolution (serum creatinine within 10% of Baseline, protein-creatinine ratio within 50% of Baseline), stabilises or becomes not clinically significant, or is assessed as being chronic.

- Liver laboratory values that require discontinuation
  - ALT or AST > 5 times the ULN
  - ALT or AST > 3 times the ULN and bilirubin total > 2 times ULN or international normalised ratio (INR) > 1.5 or the appearance of worsening fatigue, nausea, vomiting, right upper quadrant (RUQ) pain/tenderness, fever, rash, or eosinophilia

3. Pregnancy as confirmed by a positive urine test at any time during Part 1 (Acute Exacerbation Phase)
4. Clinically significant change in cardiac rhythm or other clinically significant cardiovascular abnormality or an increase in QTcF ≥ 60 msec above baseline
5. Use of prohibited treatment
6. Any other protocol deviation that results in a significant risk to the subject's safety
7. Withdrawal of informed consent.

9.3.5 Continued study participation

If premature discontinuation of investigational treatment occurs, the subject should continue to attend the follow-up visits until the end of study for collection of data on treatment failure.

The subject should NOT be considered withdrawn from the study due to interrupting or discontinuing investigational treatment. For this study it is very important to continue collecting data, especially outcome data, on all subjects whether or not they complete treatment. The investigator must determine the primary reason for the subject's premature discontinuation of investigational treatment and record this information on the treatment disposition eCRF page. The investigator and study staff must discuss with the subject, the subject's continued participation in the study and request subjects to continue attending follow-up study visits according to the study visit schedule.

If the subject cannot or is unwilling to attend the follow-up visits, all assessments for Week 26 (refer to Schedule of Assessment Table 9-1) should be performed and the site staff should request to maintain regular phone contact with the subject, or with a person pre-designated by the subject. This phone contact should preferably be done according to the study visit schedule. Data will continue to be collected concerning the subject's health status, including information regarding new / concomitant treatments, adverse events, events of special interest i.e., rash etc., and vital status.

If the subject decides to completely withdraw from the study (refuses any further study participation or contact), all study participation for that subject will cease and data to be collected at subsequent visits will be considered missing.

The appropriate personnel from the site and ICON will assess whether investigational treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

The investigator must also contact the IRT to register the subject's discontinuation from investigational treatment.

9.3.6 Discontinuation of Study Sites

Study site participation may be discontinued if Mereo BioPharma or designee, the investigator or IRB/IEC of the study site judges it necessary for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and GCP.

9.3.7 Discontinuation of Study

The study will be discontinued if Mereo BioPharma or designee, including through DMC recommendation, judges it necessary for medical, safety, regulatory or other reasons consistent with applicable laws, regulation and GCP.

9.3.8 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorised by the subject. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes or emails as well as lack of response by the subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records. Data to be collected at subsequent visits will be considered missing.

10 TREATMENT OF SUBJECTS

10.1 Identity of Study Treatment(s)

10.1.1 Administration of Study Treatment(s)

The investigational treatment BCT197 is prepared as gelatine capsules (white to near white powder in hard gelatine capsules) in doses of [redacted]. Those subjects randomised to the placebo regimen will be administered two matching placebo capsules that are identical to the test product in appearance but contain no active ingredient.

BCT197 or placebo capsules should be taken orally with fluids at the same time of the day according to the randomised regimens detailed in Table 7-1.

All subjects will be treated with test product or placebo on [redacted] after Randomisation. Subjects will be screened for not more than one day and followed daily in the

first week and on Days 10 and 14 (Acute Exacerbation Phase), and then at 8, 12 and 26 weeks in the Stabilisation Phase.

All subjects will be treated as per institution SoC, since in agreement with GOLD 2015 updated version for treating COPD exacerbations, open label corticosteroids and/or antibiotics may be administered at the investigator's discretion. Subjects will be permitted to use SoC short-acting bronchodilators as rescue medication on an 'as needed' basis.

10.2 Study Treatment Packaging and Labelling

10.2.1 Packaging

Each study site will be supplied with investigational treatment in packaging of identical appearance.

Investigator staff will identify the investigational treatment package(s) to dispense to the subject by contacting the IRT and obtaining the medication number(s). This number should be recorded in the subject's notes and in the Pharmacy file.

10.2.2 Labelling

Medication labels will comply with the legal requirements of each country and be printed in the local language. They will supply no information about the subjects.

10.2.3 Storage

Based on available stability data, [redacted] should be stored at $\leq 25°C$. The storage conditions for the study drug will be described on the medication label.

10.2.4 Blinding and Randomisation of Study Treatments

At Visit 1 all eligible subjects will be randomised via IRT to one of the treatment regimens. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfils all the inclusion/exclusion criteria. The IRT will assign a medication number to the subject which will be used to link the subject to a treatment regimen and will specify a unique medication number for the package of investigational treatment to be dispensed to the subject. The randomisation number will not be communicated to the caller.

The randomisation numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomisation list will be produced by ICON Biostatistics using a validated system that automates the random assignment of subject numbers to randomisation numbers. These randomisation numbers are linked to the different treatment regimens, which in turn are linked to medication numbers. A separate medication list will be produced using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug.

Should a situation arise where unblinding is required, the investigator at that site may perform immediate unblinding without the need for communication with the sponsor.

10.3 Procedure for Breaking the Randomisation Code

Subjects, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomisation until database lock, using the following methods:

- Randomisation data are kept strictly confidential until the time of blinding, and will not be accessible by anyone involved in the study
- The identity of the treatments will be concealed by the use of investigational treatment that is identical in packaging, labelling, schedule of administration and appearance.

Emergency treatment code breaks should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, investigational treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the ICON site monitor, the medical monitor, and the ICON Project Manager that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide the protocol number, investigational treatment name if available, subject number, and instructions for contacting the local entity which has responsibility for emergency code breaks to the subject in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

The randomisation codes associated with each subject will be disclosed to PK analysts who will keep PK results confidential until database lock.

10.4 Subject Compliance

Study drug compliance will be assessed by the investigator and/or centre personnel by recording capsule counts of study treatments from the previously dispensed blister strips. The investigator and/or centre personnel will also assess whether the subject has been given the capsules in the prescribed order. The total number of doses administered to each subject will be derived from dosing information recorded in the eCRF.

10.5 Study Treatment Accountability

Records shall be maintained of the delivery of study treatments to the study centres, the inventory at the study centres, the use of each subject and the return to the sponsor.

These records shall include dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the study medication and to the study subjects.

The investigator shall be responsible for ensuring that the records adequately document that the subjects were provided the doses specified in the protocol and that all study medication received from the sponsor is reconciled. All study medication must be returned to the sponsor or sponsor designee according to the procedures described in the Pharmacy Manual.

10.6 Concomitant Therapy

10.6.1 Permitted Concomitant Medication for COPD

1. Long-acting anti-histamines if taken at stable regimen at least 2 months prior to Screening or if taken PRN. For subjects not on stable, long-acting anti-histamines, short courses are allowed during the study period (≤ 7 days). Other anti-histamines are allowed during the study period for a short course (≤ 10 days) or if taken PRN
2. If required for respiratory symptoms or a COPD exacerbation:
    - Systemic corticosteroid (oral/IV/intramuscular)
    - Inhaled short-acting β_2-agonists and/or short acting muscarinic antagonists or combination of both
    - Nebulised β_2-agonists, anti-cholinergics and/or steroids
    - Antibiotics
    - Oxygen.
3. Mechanical ventilation at the investigator's discretion
    - Mechanical ventilation is exclusionary at Screening. However, if the subject requires mechanical ventilation during the course of the study, they should remain on the study until Week 26, even if further study drug cannot be administered or assessments carried out.
4. Short courses (≤ 10 days) of nasal corticosteroids (maximum two courses) are allowed
5. Current regular therapy for COPD as stated in inclusion criterion 8
6. Current regular theophylline.

10.6.2 Prohibited Therapy

The class of medications listed in Table 10-1 are not permitted to be taken for the specified time before dosing with study treatment. Medications excluded for Drug-Drug interaction potential (e.g. CYP3A4 inhibitors) should be excluded until Day 14. Medications excluded for potential to affect respiratory efficacy end points should be excluded for the duration of the study unless required to treat worsening of clinical condition. Live vaccines should be excluded from the time specified in Table 10-1 before dosing, during dosing and up to Week 8. Each concomitant drug must be individually assessed against all exclusion criteria and the table below. If in doubt, the investigator should contact the ICON medical monitor before randomising a subject or allowing a new medication to be started. Whilst not prohibited, killed vaccines may be less efficacious if administered in the period 14 days prior to study

drug dosing and up to Week 8. Consideration should be made to assess vaccine response and/or revaccinate during this period.

Table 10-1 Prohibited Medication

Class of medication	**Subject will not be included in the study if the following prohibited medications have been taken within**
CYP3A4 inhibiting drugs (including chloramphenicol)	14 days prior to randomisation
Ingestion of grapefruit juice	14 days prior to randomisation
CYP3A4 inducers including carbamazepine, phenytoin, rifampicin and St John's Wort	14 days prior to randomisation
Non-cardioselective β blockers	10 days prior to randomisation
Multi drug resistance protein 1 (P-gp) inhibiting drugs including the calcium channel blockers verapamil and diltiazem (with the exception of azithromycin, which is not prohibited)	14 days prior to randomisation
Monoamine-oxidase inhibitors	14 days prior to randomisation
Live attenuated vaccine	30 days prior to randomisation
Monoclonal antibodies	6 months prior to randomisation
p38 mitogen activated protein kinase inhibitor	6 months prior to randomisation
PDE3/4 inhibitors	6 months prior to randomisation
IgE inhibitors (e.g. xolair)	6 months prior to randomisation
Leukotriene antagonists and leukotriene synthesis inhibitors	7 days prior to randomisation

This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria. The washout of these prohibited medications is not to be encouraged.

11 ASSESSMENT OF EFFICACY

11.1 Efficacy Variables

1. FEV1, FVC and FEV1/FVC on Days 1 to 7 (daily), 10, 14, and at Weeks 8,12 and 26
2. FEV1, FVC and FEV1/FVC form the most recent test performed within the last 12 months outside an exacerbation
3. Time to improvement of 100 mL in FEV1 compared to Baseline versus placebo
4. AUC of FEV1
5. RR on Days 1 to 7 (daily), Days 10, 14, and at Weeks 8,12 and 26
6. EXACT-PRO score daily from Baseline up to the end of subject participation
7. AUC of EXACT-PRO
8. Number of COPD-related deaths from first dose intake up to the end of study participation (Week 26)
9. Number of moderate/severe COPD exacerbations over time among groups
10. Time to next moderate/severe COPD exacerbation (in days)
11. Number of uses of rescue therapy during the study
12. Time from hospitalisation until the subject is medically ready for discharge
13. Exploratory composite endpoints:
    - Number of events of worsening of symptoms warranting the addition of antibiotics
    - Number of events of worsening of symptoms warranting an increase of oral dose of corticosteroids or initiation of new oral corticosteroids
    - Number of events of worsening of symptoms requiring additional treatment with oral corticosteroids and/or antibiotics after completion of the initial regimen
    - Number of events of COPD exacerbations that required re-hospitalisation
    - Number of COPD-related deaths.
14. CRQ scores at Baseline, Day 14 and at Weeks 8, 12 and 26
15. Cumulative oral/IV steroid dose Days 1 to 14, and from Day 14 to Week 26
16. Blood biomarkers (IL-6, TNF-α, fibrinogen, hs-CRP, and MPO)
17. BCT197 exposure on Days 1, 3, and 5
18. Body Mass Index at Baseline, Days 7, 14, and Weeks 8, 12 and 26
19. Dyspnoea (mMRC dyspnoea scale) at Baseline, Days 7, 14, and Weeks 8, 12 and 26
20. 6MWT and BMI Day 14 (for BODE index calculation).

11.2 Efficacy Assessments

Primary

1. Change in FEV1 from Baseline (pre-dose) to Day 7.

Secondary

1. Comparison of FEV1 on Days 3, 10, and 14
2. Normalisation evaluation of spirometry parameter (FEV1, FVC and FEV1/FVC) response over time (performed daily from Days 1 to 7, 10, and 14, and Weeks 8, 12 and 26) compared with the most recent test performed within the last 12 months outside an exacerbation (pre-study FEV1, FVC, and FEV1/FVC value)
3. Time to improvement of 100 mL in FEV1 compared with Baseline versus placebo
4. Comparison of AUC of FEV1 over time among groups
5. Change in RR over time (performed daily from Days 1 to 7, 10 and 14) among groups
6. Change on RR on Day 3, 7, 10 and 14 among groups
7. Time to improvement based on EXACT-PRO total score
8. Comparison of AUC of EXACT-PRO among groups
9. Number of COPD-related deaths during the study
10. Number of moderate/severe COPD-related exacerbations during the study
11. Time to next moderate/severe COPD exacerbation
12. Change from Baseline at each inter-visit period and over the entire period of the study in the average EXACT-PRO total score and domain scores
13. Number of times each subject required rescue therapy during the study
14. Time from hospitalisation until the subject is medically ready (COPD-related) for discharge
15. Nonlinear mixed effects pharmacokinetic/pharmacodynamics (PK/PD) models evaluating the relationship between BCT197 exposure and efficacy/safety endpoints.

Exploratory

1. Exploratory composite scale endpoints comparing among the three groups at Weeks 8, 12 and 26:
    - Number of events of worsening of symptoms warranting the addition of antibiotics
    - Number of events of worsening of symptoms warranting an increase of oral dose of corticosteroids or initiation of new oral corticosteroids
    - Number of events of worsening of symptoms requiring additional treatment with oral corticosteroids and/or antibiotics after completion of the initial regimen

- Number of events of COPD exacerbations that required re-hospitalisation
- Number of COPD-related deaths.

2. Change in CRQ from Baseline at Day 14 and Weeks 8, 12 and 26 to evaluate recovery, comparing among the three groups over time
3. Cumulative oral/IV steroid dose from Day 1 to Day 14, and from Day 14 to Week 26
4. Change in inflammatory blood biomarkers (IL-6, TNF-α, fibrinogen, hs-CRP, and MPO) daily during Part 1 of the study, and at Weeks 8, 12 and 26
5. Relationship between BCT197 exposure and efficacy/safety endpoints
6. Change from Baseline in mMRC dyspnoea scale over time
7. BODE index among the three groups at Day 14.

11.2.1 Spirometry

Pulmonary function tests will be carried out under medical supervision in either a clinic or hospital and will be recorded using a computer-operated spirometer.

Lung function measurements and daily calibration of the spirometer will be done to the recommendations of the official Statement of the European Respiratory Society (ERS) and the American Thoracic Society (ATS). All sites will be provided with equipment and a central spirometry laboratory will be used. Investigator sites will be trained to the use of the system during the investigator meeting. All calibration reports should be printed and kept with the source study documents.

The specific procedures for the central spirometry will be provided to the investigator by the central spirometry company.

Forced Expiratory Volume in the 1st second in litres (FEV1, L) and Forced Vital Capacity (FVC, L) will be recorded daily from Days 1 to 7 and on Days 10 and 14 during Part 1 of the study and at all visits of the Part 2 of the study. At either Week 8, 12, and 26 pre and post bronchodilator spirometry will be performed, for demographic purposes, if this information is not available from historical spirometry. This is additional to the 'on bronchodilator' spirometry, with the 'on bronchodilator' measurement being the priority.

The chosen value should not exceed the next by more than 150 mL. If the difference is larger, up to 8 measurements will be made and the highest value reported. The ratio FEV1/FVC will be derived from this highest value of each parameter.

Predicted values will be automatically calculated with the demographics data recorded in the centralised system.

If more than one spirometry has been conducted within the 12 months before the study the most recent result, outside the exacerbation, will be used as the pre study value.

11.2.2 Body mass index, airflow obstruction, dyspnoea, and exercise (BODE) index

BMI

The BMI is to be calculated from the weight and height obtained at Day 14 where the BODE index is required. BODE uses the binary classification for BMI > 21 kg/m^2 or ≤ 21 kg/m^2.

Obstruction

The level of obstruction for the BODE index will be collected from the spirometry done at the time points where the BODE index is specified. The index to be used is the FEV1% (in relation to the predicted value).

Dyspnoea (mMRC score)

The mMRC dyspnoea scale is a questionnaire that consists of five statements about perceived breathlessness: grade 0, "I only get breathless with strenuous exercise"; grade 1, "I get short of breath when hurrying on the level or up a slight hill"; grade 2, "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"; grade 3, "I stop for breath after walking 100 yards or after a few minutes on the level"; grade 4, " I am too breathless to leave the house".

The investigator or his designee who will apply the mMRC should orient how the scale is graded, explain to the subject that he/she should choose the one option that best reflects the current dyspnoea limitation and then let the subject choose his/her own score without any suggestion or interference by the investigator/designee.

Exercise (6MWT)

The 6MWT to achieve the BODE index will be performed at Day 14 when BODE index is required. It will be documented if it is not medically possible for the subject to perform the 6MWT. The subject will be required to walk as fast as he/she can without stopping for 6 minutes, in a pre-defined and scaled circuit supervised by a physician and with oxygen saturation monitoring. This test should follow the ATS 2002 guidelines for 6MWT. The ATS guidelines for the 6MWT recommend use of a 30-metre or 100-foot walkway with the length of the corridor marked every 3 metres. Turnaround points should be marked by a cone or similar to avoid interruption during the test (ATS, 2002).

The distance covered over 6 minutes will be recorded as well the speed (if available) and the oxygen saturation.

Assistive devices can be used but must be kept consistent from test to test; the subject may use a device but should be able to walk without physical assistance.

BODE Index

The BODE index is used to evaluate the functional status of subjects with COPD. It will be assessed at Day 14. Each parameter of the index (obstruction, dyspnoea score per mMRC and exercise through the 6MWT) is graded from 0 to 3 with the exception of BMI which is graded as 0 or 1. The overall BODE score can vary from 0 to 10.

11.2.3 COPD exacerbations

A COPD exacerbation is defined as *"A sustained worsening of the patient's condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics* ***or*** *need for hospitalisation"*.

The exacerbations will be classified as moderate or severe as per the EMA/CHMP guideline definition:

- Moderate: exacerbations that require treatment with systemic corticosteroids and/or antibiotics.
- Severe: Exacerbations that require hospitalisation or result in death.

Emergency room (ER) attendance includes any unscheduled visit at any healthcare institution requiring urgent advice associated with systemic steroids (addition or increment of dose). If an ER stay is longer than 24 hours it will be considered severe. If the ER visit is shorter than 24 hours and not related to any prescription of systemic steroids or antibiotics it will not be considered moderate or severe exacerbation.

For the Screening Visit, a current active COPD exacerbation is classified as one that requires hospitalisation, systemic corticosteroids (start of systemic corticosteroid, or increase in the dose of the systemic corticosteroid) and/or antibiotics.

For the documented history of COPD, moderate and severe COPD exacerbations are defined above. Documentation of previous COPD exacerbation could be, but is not limited to, ER or hospital discharge summary, source document notes at the time of the exacerbation, reference letter from the attending physician of the COPD exacerbation, or the medical prescription of the previous COPD exacerbation with antibiotics or systemic steroids prescribed.

For Part 2 (Stabilisation phase) of the study, COPD exacerbation will be considered all moderate and severe COPD exacerbations per the definition above. Exacerbations that do not fulfil these criteria should be reported as an AE (e.g. worsening of symptoms). A COPD exacerbation during Part 2 of the study is not a reason to withdraw the subject from the study, unless deemed necessary by the investigator.

11.2.4 Number of COPD-related deaths

The number of COPD-related deaths will be determined at the end of the study. It is the responsibility of the investigator to define whether death was COPD-related. The rationale used in this causality assessment should be recorded in the source documents and in the eCRF.

11.2.5 Exploratory composite endpoints

These endpoints are to be collected in the subject's eCRF at Day 14, and Weeks 8, 12 and 26.

This evaluates treatment failure as defined by:

1. Worsening of symptoms warranting the addition of antibiotics

2. Worsening of symptoms warranting an increase in dose of oral corticosteroids or initiation of new oral corticosteroids
3. Worsening of symptoms requiring additional treatment of oral corticosteroids and/or antibiotics after completion of the initial regimen
4. Re-hospitalisation due to worsening of COPD and requiring additional treatment during the duration of the study due to exacerbations of respiratory symptoms
5. COPD-related death.

11.2.6 Chronic Respiratory Questionnaire

The CRQ is used to evaluate four dimensions: dyspnoea, fatigue, emotional function, and mastery (the subject's feeling of control over their disease). The questions covering the dimensions of fatigue, emotional function, and mastery are standardised and the subject is offered an appropriate 7-point scale for each question. The dyspnoea component is not standardised. The subject is required to identify everyday activities which make them breathless and then select, rank, and score the five most important activities on a 7-point scale which spans from 1 (extremely short of breath) to 7 (not at all short of breath). Every subject will have a unique list of activities. In each dimension the lower the score, the greater the degree of dysfunction.

An interviewer administered standardised CRQ will be used for the study. The investigator or designee who will apply the CRQ should orient how the scale is graded, explain to the subject that he/she should choose the one option that better reflects the current dyspnoea limitation and then let the subject choose his/her own score without any suggestion or interference by the instructor.

The score will be applied at Baseline at Day 14, and Weeks 8, 12 and 26 and will allow an evaluation of the improvement of subject well-being throughout the study.

11.2.7 Blood Biomarkers

Blood biomarkers (IL-6, TNF-α, fibrinogen, hs-CRP, and MPO) will be measured on Days 1 to 7, and Days 10 and 14 during Part 1 of the study, and at Weeks 8, 12 and 26.

11.2.8 EXACT-PRO

The EXACT is a 14-item patient reported outcome (PRO) daily diary used to quantify and measure exacerbations of COPD (Mackay 2014). This instrument provides a single, standardised approach for assessing the symptomatic manifestations of COPD exacerbations, with a development and validation history consistent with guidelines proposed by the Food and Drug Administration (FDA), EMA and well-known measurement principles.

The questionnaire is composed of 14 items covering various domains such as breathlessness, cough and sputum, chest symptoms, and overall status (tiredness, weakness, sleep disturbances). Each question is individually weighted to provide a total score varying from 0 to 100. The health status of the subject is correlated to the global score, meaning a higher score corresponds to a more severe health status of the subject.

The EXACT-PRO will be completed once a day in the evening by the subject. The EXACT score will be monitored and will raise an alert to the investigator in case of relevant increases.

11.3 Pharmacokinetics

Sparse PK sampling for BCT197 and metabolite(s) (4 samples) will be done on any 2 of the 3 dosing occasions: one sample will be taken pre-dose, one between 0 and 2 hours post-dose, one between 4 and 8 hours post-dose and one no earlier than 12 hours post-dose.

12 ASSESSMENT OF SAFETY

The timing and frequency of safety assessments are described in Section 9.1.2 and Section 9.1.3.

12.1 Adverse Events

12.1.1 Definitions

The definitions for AEs and SAEs are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse Event/Reaction

An AE is defined as any untoward medical occurrence in a subject, or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Any relevant observations made at the Screening Visit (prior to signing the ICF) are to be recorded as a pre-existing condition; an AE will only be recorded if there is a worsening of the pre-existing condition during study conduct with regards to nature, severity, or frequency.

An adverse drug reaction is an "untoward and unintended response to an investigational medicinal product related to any dose administered".

All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression of "reasonable causal relationship" means to convey in general that there are facts or arguments meant to suggest a causal relationship.

Serious Adverse Event

An SAE is defined as an AE that results in one of the following outcomes:

1. Results in death

   Death is not an adverse event itself, but an outcome. The cause of the death is currently the AE which resulted in death.

2. Is life-threatening

   Life-threatening means that the subject was at immediate risk of death at the time of the SAE, it does not refer to a SAE that hypothetically might have caused death if it were more severe.

3. Requires in-patient hospitalisation or prolongs existing hospitalisation (This does not include prolonged hospitalisation for study purposes)

   Hospitalisation is defined as at least one overnight formal admission into hospital, usually to perform additional tests, provide treatment that it is not possible to provide at

home and/or to allow specific monitoring of the subject due to their unstable medical condition. Current hospitalisation due to the COPD and pre-planned hospitalisations (known already prior to signing the ICF) will not be considered an SAE, unless any of the above criteria are fulfilled over the course of the hospitalisation due to unplanned complications. Following the initial discharge from hospital, subsequent hospitalisations due to COPD are to be considered an SAE. "Social" hospitalisation, defined as administrative impossibility to discharge the subject is not necessarily an SAE. Complications that occur during hospitalisation are AEs unless they would qualify as an SAE for any of the above criteria. If the complication delays the subject's release from hospital, then the AE becomes an SAE. Hospitalisations due to diagnostic procedures which are not performed due to an AE are not regarded as SAE.

4. Results in persistent or significant disability/incapacity

   The term significant disability refers to any condition that impairs physical/psychological well-being to the extent that the subject is unable to function normally. Physical disability may include, but is not limited to, permanent disability of locomotion or motility, but also systemic permanent dysfunction as development of heart failure, liver insufficiency or pulmonary fibrosis.

5. Is a congenital anomaly/birth defect

6. Is an important medical event

   Important medical events that may not result in death, be life-threatening or require hospitalisation may be considered an SAE, when based on appropriate medical judgement, they may jeopardise the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Treatment Emergent Adverse Event (TEAE)

TEAEs are defined as any AE occurring or worsening on or after the first dose of study medication.

Adverse Events of Special Interest (AESI)

Refer to Section 12.1.7.

12.1.2 Recording of Adverse Events

Any relevant observations made at the Screening Visit (prior to signing the ICF) are to be recorded as a pre-existing condition. For the purposes of this study, any detrimental change in the subject's condition, after signing the informed consent form and up to completion of the 26 week follow-up period after the last administration of study drug, should be considered an AE/SAE.

The following variables will be recorded for each AE: verbatim/AE description and date for AE start and stop, severity, seriousness, causality rating, whether or not the AE caused the subject to discontinue, and the outcome. If the severity of the AE changes, a new AE must be recorded.

SAEs and AEs will be recorded starting after signing of informed consent. All SAEs and AEs have to be recorded, whether or not considered causally related to the investigational product or to the study procedure(s).

All ongoing AEs/SAEs should be followed up until resolution or stabilisation or the last visit if in the investigator's opinion, the AE is unlikely to resolve due to the subject's underlying disease.

At any time after the follow-up visit, if an investigator learns of an SAE that can be reasonably related to study drug, he/she should promptly notify the sponsor.

The investigator will assess the intensity of AEs based on the following definitions:

1. Mild (awareness of sign or symptom, but easily tolerated)
2. Moderate (discomfort sufficient to cause interference with normal activities)
3. Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 12.1.8.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study drug and the AE.

12.1.3 Causal Assessment

The following “binary” decision choice will be used by the investigator to describe the causality assessment:

- Reasonable possibility of a relatedness
- No reasonable possibility of relatedness.

The term “reasonable possibility of relatedness” is meant to convey, in general, that there is enough evidence or argument to suggest the causal relationship. The investigator should consider, before reaching up to a decision on causality assessment:

- Time relationship between study drug intake and event’s onset
- Dechallenge
- Rechallenge
- Medical History
- Study treatment
- Mechanism of action of study drug
- Class effect

- Concomitant treatments in use
- Withdrawal of study treatment
- Lack of efficacy/worsening of existing condition
- Erroneous treatment with study medication or concomitant medication
- Protocol related process.

Action taken with study drug due to the AE:

- None
- Drug permanently discontinued
- Unknown/not applicable.

Other action taken:

- Specific therapy/medication
- Surgical medical procedure
- (Prolonged) hospitalisation.

Outcome

Each single AE must be rated by choosing one of the following:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal
- Unknown.

12.1.4 Abnormal Laboratory Values/Vital Signs/Electrocardiograms

Laboratory/vital signs/ECG abnormalities should be reported as an AE/SAE if any one of the following criteria is met:

1. Result is clinically significant or associated with signs/symptoms
2. Requires additional diagnostic testing and/or interventions
3. Leads to a change in dose, discontinuation of or interruption to the study drug.

Repeats of an abnormal test result without any of the above criteria do not constitute an AE. Any test result determined to be an error is not required to be reported as an AE.

12.1.5 Overdose

A drug overdose is defined as the accidental or intentional use of a drug or medicine in an amount that is higher than is normally used. Every overdose must be reported to ICON Medical and Safety Services (MSS) within 24 hours of awareness, irrespective of whether the overdose was associated with an AE/SAE. In case of overdose in which decreasing the systemic concentration of BCT197 may be deemed as being of possible clinical benefit, the investigator should consider haemodialysis or other filtration method to decrease the systemic concentration. This is based on BCT197 being a small molecule with low protein binding and moderate volume of distribution.

12.1.6 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. If a pregnancy is reported for a subject, no further study drug will be administered to this subject and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented. Follow-up should be done up to delivery and after the examination of the newborn when a follow up report should be sent with any new information regarding the pregnancy and the outcome of the newborn.

All congenital abnormalities/birth defects should be classified as SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs, but should be reported as an AE. All outcomes of pregnancy must be reported to the sponsor on a pregnancy outcomes report form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

Pregnancies must be reported to ICON MSS using the reporting details provided in Section 12.1.8 within 24 hours of awareness.

12.1.7 Adverse Event of Special Interest

Some AEs, despite their severity or outcome, will be expedited due to the relevance for subject safety or study drug safety profile. These events should be reported to ICON MSS within 24 hours of awareness:

1. Pneumonia
    - The diagnosis of pneumonia should be confirmed with a chest radiography (two positions) or a CT scan. Whenever possible, microbiologic confirmation should be obtained and the corresponding form in the eCRF should be completed.

2. Liver injury
    - For subject safety and to ensure that the hepatotoxic potential of the study drug can be determined, a standardised procedure for identification, monitoring and evaluation of liver events must be followed:
        a) In the event of: i) ALT or AST elevations > 5 x ULN or ii) ALT or AST > 3 x ULN and bilirubin total > 2 x ULN or INR > 1.5 or the appearance of worsening fatigue, nausea, vomiting, RUQ pain/tenderness, fever, rash, or eosinophilia, the study drug should be withdrawn and testing repeated within 2 days. An investigation of the liver event should be carried out in order to evaluate other causes for liver injury. These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. The subject should be hospitalised if required. The appropriate form in the eCRF should be completed.
        b) In the case of ALT and AST elevations < 5 x ULN or ALT and AST < 3 x ULN and bilirubin total < 2 x ULN, the tests should be repeated to confirm the elevation and report as an AE if clinically significant.

3. Dermatologic events (Rash/Acneiform dermatitis/Pruritus)
    - The appropriate diagnosis should be confirmed with a dermatologist evaluation and appropriate treatment provided to the subject. The corresponding eCRF form should be completed.

4. Headache
    - If the event starts during the study, the corresponding eCRF form should be completed. Subjects who have a migraine or tension headache will fulfil this criteria only if it is noted as a worsening in the frequency or intensity.

5. Inflammation of cervix and vagina
    - If the event starts during the study, the corresponding eCRF form should be completed. The diagnosis should be confirmed with a gynaecologist evaluation and appropriate treatment provided to the subject. The gynaecologist assessment should be recorded in the source documents and a summary of the findings recorded in the eCRF.

12.1.8 Reporting of Serious Adverse Events and Adverse Events of Special Interest

Investigators and other site personnel must inform ICON MSS of any SAE/AESI that occurs (whether or not attributable to the study drug) during the course of the study (from the time of informed consent until the End of Study Visit) within 24 hours of when he or she becomes aware of it.

Follow-up information on SAEs/AESIs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to ICON MSS within 24 hours as described above.

All SAEs/AESIs must be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs/AESIs will also be recorded in the eCRF. The investigator is responsible for informing the Ethics Committee of the SAE/AESI as per local requirements.

Paper SAE/AESI forms should be completed at the site and faxed to the relevant MSS Department at ICON Clinical Research or e-mailed to the global email distribution list **within 24 hours** of awareness of the event.

SAE/AESI reports should be sent by all participating investigational sites to the following email address:

STUDY-MSS-DL-3082-0004-Global@iconplc.com

If the report is sent via email then the completed and signed SAE/AESI or Pregnancy report form must be attached to the email. A notification email of the event describing it in the email text is not sufficient.

Alternatively, the following fax numbers can be used for transmission of the completed SAE/AESI reporting form:

For European sites:

Telefax: +49 (0) 6103 904 217

For North and South American sites

Telefax: + 1 215-240-6991

There may be situations when an SAE/AESI has occurred and the investigator has minimal information to include in the initial SAE/AESI report. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE/AESI report form. Minimum criteria are identifiable subject (number), a suspect product (i.e. study drug or concomitant medication), an identifiable reporting source (investigator/study site identification), and an event or outcome that can be identified as serious or as an AESI. The investigator may change his/her opinion of causality in the light of follow-up information, amending the SAE/AESI report form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements for SAEs.

Suspected Unexpected Serious Adverse Reactions (SUSARS) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national requirements in participating countries.

12.2 Safety Endpoints

Assessment will include assessment of:

1. TEAEs/SAEs (from first dose of study drug until study completion)
2. TEAEs of special interest (pneumonia)
3. TEAEs of special interest (liver enzymes [ALT, AST, bilirubin total and fractions], rash, acneiform dermatitis, cervical/vaginal inflammation, headache and pruritus)
4. Vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure)
5. QTc intervals and ECG findings (arrhythmias, conduction blocks, changes in ST segment) at Baseline, from Day 1 to Day 7, Days 10 and 14
6. Laboratory data including sputum cultures and blood eosinophil percentages.

12.3 Laboratory Assessments

Haematology, blood chemistry, and urinalysis will be conducted at Screening, on Days 1, 3, 5, 7, 10 and 14, and at each visit in the Stabilisation phase.

Haematology, blood chemistry and pregnancy tests done at the Screening visit of the study should be sent to both the local laboratory and central laboratory for analysis. Haematology, blood chemistry and pregnancy done at all other visits of the study should be sent only to the central laboratory for analysis, with the exception of urine dipstick pregnancy test that should be done at the local laboratory.

Local laboratory normal ranges will be collected prior to first patient first visit (FPFV) at each site and provided to data management via the study team. Laboratory results collected from the local laboratory should be entered in the eCRF by the investigator.

The following parameters will be assessed:

- Haematology: red blood cell count, white blood cell count with differential counts and percentages, total haemoglobin, haematocrit, platelets count, INR and prothrombin time (INR and prothrombin time not required during the Stabilisation phase)
- Blood chemistry: creatinine, blood urea nitrogen [BUN], fasting serum glucose, AST, ALT, gamma-glutamyl transpeptidase, total bilirubin, albumin, chloride, calcium, phosphorous, uric acid, total protein, sodium and potassium
- Urinalysis (specific gravity, pH, protein, glucose, blood)
- Pregnancy test: serum β-HCG and urinary pregnancy test.

Blood collection and sample preparation will be performed according to procedures from the local and central laboratories.

If sputum or bronchoalveolar culture is collected for any medical reason (qualitative or quantitative culture), the result should be recorded in the eCRF and included in the safety analysis.

12.4 Medical Evaluation/Physical Examination

A full medical evaluation and physical examination should be performed at each visit in order to evaluate the medical condition of the subject and also detect any sign/symptom of AEs, and to perform all the procedures required per protocol. Height will only be measured at the Screening Visit.

12.5 Vital Signs

Vital signs include body temperature, systolic and diastolic blood pressure, pulse, blood oxygen (using a pulse oximeter), and respiratory rate. After the subject has been sitting for five minutes with back supported (in a chair or in bed), pulse rate and systolic and diastolic blood pressure will be measured. Respiratory rate will be measured after the subject has been resting for 10 minutes.

12.6 12-lead ECG

The 12-lead ECG measurement will be done under medical supervision in either a clinic or hospital at all visits. All sites will be provided with equipment and a central ECG laboratory will be used. Investigator sites will be trained in the use of the system.

ECG should be done before any blood sample collection scheduled for the same time.

Before recording, subjects should be resting in a quiet supervised setting with minimal stimulation (e.g. no television, loud music, computer games) and lie in a resting position for 10 minutes before ECG recording.

QTc value will be calculated using the Fridericia formula ($QTc=QT/\sqrt[3]{RR}$). The QTc interval will be automatically calculated.

In the case of clinically significant ECG abnormalities, the investigator should report these as an AE if not due to a pre-existing condition or if a pre-existing condition worsens in frequency or intensity.

12.7 24/7 Medical Emergency Coverage

In a study related emergency situation, when the assigned Medical Monitors for a study cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an ICON Call Centre:

- Telephone: +1 919 674 5468

(chargeable telephone number allowing a global reach from both landlines and mobile phones)

- https://icophone.iconplc.com

On this internet page, a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the "24/7 Medical Helpdesk" index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

12.8 Data Monitoring Committee (DMC)

An independent, external DMC will periodically review accumulating safety data. Full details of composition, operational aspects, and data to be reviewed and recommendation to be made by the DMC will be described in a separate DMC charter.

12.9 Independent Adjudication Committee (IAC)

Once subjects have completed study treatment, all new reports of exacerbation of COPD and events of hospitalisations due to new exacerbations of COPD will be evaluated by an external IAC. Specific details regarding procedures for clinical adjudication of the components of the endpoint will be described in a separate charter.

13 STATISTICAL EVALUATION

13.1 Sample Size and Power

The sample size is based on a formal statistical calculation using the following assumptions:

1. Endpoint: Change in FEV1 from Baseline to Day 7
2. Minimum clinically significant difference between regimens: 100 mL
3. Standard deviation = 230 mL (based on a previous study [CBCT197A2201] with BCT197)
4. Superiority design of two BCT197 doses compared to placebo
5. Two-sided alpha (Type 1) error = 0.05
6. No adjustment for multiplicity
7. Beta error (Type 2) = 0.20 (Power = 80%).

Based on the above assumptions, 85 subjects will need to be analysed per dose regimen, resulting in a total of 255 evaluable subjects.

Assuming a dropout rate of approximately 5%, a total of approximately 270 subjects will be randomised to the study.

13.2 Randomisation

ICON Biostatistics will prepare the randomisation list based on a randomisation scheme blocked by site. Each subject will be assigned to one of three dosing regimens defined in Section 10.1.1 in a 1:1:1 ratio.

See Section 10.2.4 for further details of the Randomisation procedures to be applied.

13.3 Analysis Sets

All primary and secondary efficacy endpoints will be analysed using the intention to treat (ITT) population. The per protocol (PP) population will be used only for the analysis of the primary endpoint to examine the robustness of the primary analyses.

Safety and tolerability will be analysed using the safety population.

Pharmacokinetic data will be analysed using the PK population.

13.3.1 Intention to treat (ITT) (Full Analysis Set)

The intention to treat population includes all subjects who:

1. Are randomised, and
2. Receive at least one dose of study medication, and
3. Provide a Baseline and at least one post-Baseline FEV1 value.

13.3.2 Per protocol (PP)

The PP population is a subset of the ITT population and includes all randomised subjects as randomised who have been treated according to the protocol and fulfil the following criteria (to be further described in the statistical analysis plan [SAP]):

1. All inclusion/exclusion criteria satisfied
2. Absence of relevant protocol violations with respect to factors likely to affect the efficacy of treatment where the nature of protocol violation will be defined before breaking the blind
3. Adequate study medication compliance
4. Adequate measurement of the primary variable.

13.3.3 Safety population

The safety population includes all subjects who received at least one administration of the study medication.

13.3.4 PK population

For the nonlinear mixed effects modelling, all subjects who received at least one administration and have at least one quantifiable concentration will be included.

13.4 Endpoints

13.4.1 Primary Efficacy Endpoint(s)

The primary assessment of efficacy will be made based on the change in FEV1 between Baseline (pre-dose) and Day 7.

13.4.2 Secondary Efficacy Endpoint(s)

Efficacy will be further assessed based on the following secondary endpoints:

1. Comparison of FEV1 on Days 3, 10, and 14
2. Normalisation evaluation of spirometry parameter (FEV1, FVC and FEV1/FVC) response over time (performed from Days 1 to 7, 10, 14, and at Weeks 8, 12 and 26) compared with the most recent test performed within the last 12 months outside and exacerbation (pre-study FEV1, FVC, and FEV1/FVC value)
3. Time taken to improvement of 100 mL in FEV1 compared to Baseline versus placebo
4. Comparison of AUC of FEV1 over time among groups
5. Change in RR over time (performed daily from Days 1 to 7, 10 and 14) among groups
6. Change in RR on Days 3, 7, 10 and 14 among groups
7. Time to improvement based on EXACT-PRO total score
8. Comparison of AUC of EXACT-PRO over time among groups
9. Number of COPD-related deaths during the study

10. Number of moderate/severe COPD-related exacerbations during the study
11. Time to next moderate/severe COPD exacerbation
12. Change from Baseline at each inter-visit period and over the entire period of the study in the average EXACT-PRO total score and domain scores
13. Number of times each subject required rescue therapy during the study
14. Time from hospitalisation until the subject is medically ready (COPD-related) for discharge
15. Nonlinear mixed effects PK/PD models evaluating the relationship between BCT197 exposure and efficacy/safety endpoints.

More details and the time points for collection are given in Section 9.1.3 and in the Schedule of assessments (Table 9-1). A complete list of efficacy endpoints is given in Section 11.2.

These secondary efficacy parameters will be assessed using the ITT population.

13.4.3 Exploratory Endpoints(s)

The following data were collected as exploratory endpoints:

1. Exploratory composite scale comparing the following among the three groups at Week 8, 12 and 26:
    - Number of events of worsening symptoms warranting the addition of antibiotics
    - Number of events of worsening symptoms warranting an increase in dose of oral corticosteroids or initiation of new oral corticosteroids
    - Number of events of worsening symptoms requiring additional treatment of oral corticosteroids and/or antibiotics after completion of the initial regimen
    - Number of events of COPD exacerbation requiring re-hospitalisation
    - Number of COPD-related deaths.
2. Change in CRQ from Baseline at Day 14 and Weeks 8, 12 and 26 to evaluate recovery, comparing among the three groups over time
3. Cumulative oral/IV steroid dose from Day 1 to Day 14, and from Day 14 to Week 26
4. Change in inflammatory blood biomarkers (IL-6, TNF-α, fibrinogen, hs-CRP, and MPO) daily during Part 1 of the study, and at Weeks 8, 12 and 26
5. Relationship between BCT197 exposure and efficacy/safety endpoints
6. Change from Baseline in mMRC overtime
7. BODE index among the three groups at Day 14.

13.4.4 Safety Endpoint(s)

The following data will be collected for assessment of safety:

1. TEAEs/SAEs (from first dose of study drug until study completion)
2. Evaluation of the incidence of pneumonia from first dose of study drug until completion
3. TEAEs of special interest (liver enzymes [ALT, AST, bilirubin total and fractions]; rash, acneiform dermatitis, cervical/vaginal inflammation, headache and pruritus)
4. Vital signs (body temperature, RR, pulse rate, blood oxygen [measured using a pulse oximeter], systolic and diastolic blood pressure) and laboratory parameters
5. QTc intervals and ECG findings (arrhythmias, conduction blocks, changes in ST segment) at Baseline, from Days 1 to 7, 10 and 14
6. Laboratory data including sputum cultures and blood eosinophil percentages.

These safety parameters will be assessed using the safety population. A complete list of efficacy endpoints is given in Section 11.2.

13.5 Description of Statistical Analyses

13.5.1 General Considerations

The statistical evaluation will be performed by ICON using SAS®, Version 9.3 or later. Data will be analysed by either enumeration of subjects displaying distinctive characteristics within each treatment regimen or by descriptive statistical summaries such as means, SD, medians, and ranges for continuous measures. Categorical variables will be presented by the number of observations and absolute and relative (%) frequency.

For efficacy data, summary statistics (N, mean, SD, median minimum and maximum for continuous data, and N [%] for categorical data) will be presented at each visit.

Similarly, changes from Baseline (or percentage change from Baseline if appropriate) will be summarised in a similar manner.

The main population for efficacy analysis will be the ITT population.

Unless stated otherwise, the Baseline value for a variable will be the latest value taken prior to the first dose of study medication.

Data in summary tables will generally be presented on an Observed Cases basis.

Unless stated otherwise, all statistical tests will be two-sided and conducted at the 5% level, and all quoted confidence intervals will be two-sided 95% confidence intervals. All three treatment regimens will be assessed by pairwise comparisons, no adjustment for multiplicity will be made and all analyses will be considered as exploratory analyses.

Full details of the statistical analysis will be given in the SAP.

13.5.2 Analysis of Primary Endpoint

FEV1 results (absolute values and changes from Baseline) will be summarised by treatment regimen and visit. Formal statistical analysis will be restricted to data collected up to and including Day 7.

The primary analysis of efficacy will be performed with the ITT population. Additionally for exploring the robustness of the intent-to-treat results, a supportive analysis using the PP population will be carried out.

Change of FEV1 from Baseline up to and including Day 7 will be assessed with a mixed-model repeated measures (MMRM) analysis, with treatment regimen as a factor and Baseline FEV1 as a covariate. The adjusted mean difference between regimens will be presented along with 95% confidence intervals for the Day 7 time-point.

13.5.3 Analysis of Secondary Endpoints

The analysis of secondary efficacy endpoints will be performed on the ITT population.

For the secondary efficacy endpoints, data will be summarised by treatment regimen and visit.

For each continuous parameter, change from Baseline will be assessed with a MMRM analysis, with treatment regimen as a factor and the Baseline value as a covariate. The adjusted mean difference between treatments will be presented along with a 95% confidence interval for the time-points of interest.

The proportion of subjects with a COPD-related death will be summarised and compared between treatment regimens using Fisher's Exact Test.

The pharmacokinetic parameters will be summarised by dose group and visit day.

A more detailed description will be presented in the SAP.

13.5.4 Analysis of Exploratory Endpoints

13.5.4.1 Population PK/PD modelling

Nonlinear mixed effects modelling will be utilised to develop a population PK model for BCT197 from which exposure metrics will be derived, which will be used subsequently to explore exposure-response (E-R) relationships with selected exposure and efficacy/safety endpoints.

A separate Modelling and Simulation Analysis Plan (MSAP) will be prepared and results from the PK/PD modelling will be reported separately from the CSR.

13.5.5 Safety Analyses

The analysis of safety parameters will be based on the safety population. In general, missing safety data will not be replaced. A more detailed description will be presented in the SAP.

Adverse Events

Adverse events will be coded using the most recent version available of the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be by system organ class

and preferred term. TEAEs are defined as any AE occurring or worsening on or after the first dose of study medication. If a subject experiences the same preferred term multiple times, the event will be counted only once and by the greatest severity.

The frequency and incidence of treatment emergent adverse events will be presented by system organ class and preferred term for each treatment regimen (number and percentage of subjects experiencing at least one AE per preferred term as well as the number of observed events per preferred term). Separate tables will be presented by severity and by relationship. All AEs will be presented in full in a comprehensive listing including subject number, treatment regimen, severity, seriousness, action taken, outcome, relationship to treatment, onset/stop and duration. Details of SAEs and AEs leading to withdrawal will be listed separately.

Concomitant Medication
Concomitant medication will be tabulated and summarised by treatment regimen.

Physical Examination
Physical examination results will be listed by subject and body system.

Vital signs

Vital signs will be summarised as actual values and change from Baseline by treatment regimen and visit.

ECG

The overall ECG interpretation will be summarised by presenting the number and percentage of subjects with "Normal" "Abnormal, not clinically significant" and "Abnormal, clinically significant".

ECG parameter values (e.g. QTcF) will be summarised as actual values and change from Baseline by treatment regimen and visit.

Clinical Laboratory

Descriptive statistics will be presented for quantitative laboratory parameters for each treatment regimen and time-point. Similarly, changes from Baseline will be summarised.

Values outside the normal range will be categorised as H (above the normal range) or L (below the normal range) based on the laboratory's reference range and these will be flagged in the listings of individual subject data.

Withdrawals

Subjects who withdraw from the study will be summarised by treatment regimen according to their reason for withdrawal.

13.5.6 Analysis of Further Endpoints

Demographic data and subjects' characteristics at Screening will be listed and summarised using descriptive statistics. Formal statistical analysis will not be performed on Baseline demographic data.

Medical history will be coded using MedDRA. An incidence table by body system and preferred term will be presented by treatment regimen.

Compliance with study medication will be summarised descriptively by treatment regimen.

13.6 Interim Analysis

No interim analysis is planned.

14 DIRECT ACCESS TO SOURCE DATA/NOTES

The investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and regulatory inspection.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Conduct of the Study

ICON shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2013) and all revisions thereof, and in accordance with FDA regulations (CFR, Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95).

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject non-evaluable.

15.2 Study Monitoring

The investigator shall permit the ICON Site Monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The investigator shall access medical records for the Monitor in order that entries in the eCRF may be verified. The investigator, as part of his/her responsibilities, is expected to co-operate with ICON in ensuring that the study adheres to GCP requirements.

The investigator may not recruit subjects into the study until such time that a visit, or with the agreement of the sponsor, attendance at the investigator meeting, has been made by a sponsor/ICON monitor to conduct a detailed review of the protocol and eCRF.

16 ETHICS

16.1 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC/IRB. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with FDA, ICH GCP and local requirements as applicable.

The IEC/IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures (e.g., advertisements), written information to be provided to the subjects, Investigator's Brochure, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IEC/IRB and Regulatory Authority (Competent Authority) as applicable.

16.2 Written Informed Consent

The nature and purpose of the study shall be fully explained to each subject (or their legally responsible guardian).

Written informed consent must be obtained from each subject (or guardian) prior to any study procedures being performed. The process of obtaining informed consent must be documented in the subject source documents.

The consent documents to be used for the study shall include all the elements of informed consent in accordance with FDA, ICH GCP and local requirements as applicable and be reviewed and approved by the appropriate IEC/IRB prior to use.

17 DATA HANDLING AND RECORD KEEPING

17.1 Case Report Forms/Source Data Handling

All required study data must be entered in the eCRF created for the study. This data collection tool is a validated electronic data capture (EDC) system that contains a system generated audit trail. Data required according to this protocol are recorded by investigational site personnel via data entry into the internet based EDC software system. The investigator shall ensure that all data from subject visits are promptly entered into the eCRFs in accordance with the specific instructions given. The investigator must sign each eCRF to verify the integrity of the data recorded. All internal ICON and external investigational site personnel seeking access to the eCRF are supported by a Service Desk (if applicable). At the end of the study all data captured electronically will be provided to the investigator on CD-ROM for archiving at the investigational site.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. If a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analysed at that laboratory.

The investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and physical examination reports. All information in the eCRF must be traceable to the source documents in the subject's file.

Data such as the CRQ and EXACT-PRO may be recorded directly in the eCRFs (i.e., no prior written or electronic record of data) and considered to be source data.

17.2 Retention of Essential Documents

The investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

18 FINANCING AND INSURANCE

The sponsor shall carry an insurance policy to cover compensation of subjects' health injuries arising from the study. If a subject incurs a study-related injury, the subject may be treated (and other necessary measures taken) at the study site and/or another medical institution. If it is necessary to compensate for the treatment, the sponsor will cover the cost. The sponsor shall not impose on the subject the burden of proving the causal relation between the study and the injury.

If any of the following is confirmed, the sponsor may refuse or restrict the payment of the compensation:

1. A serious GCP or protocol deviation by the investigator or sub-investigator (except deviation medically necessary to avoid an immediate hazard to study subjects)
2. Intentional act or negligence on the part of the investigator or sub-investigator or malpractice thereby
3. Injury caused by unlawful act or delinquency of a third party
4. Injury caused by intentional act or negligence of the subject.

If compensation becomes necessary for a study-related injury, the site will promptly notify the sponsor and will co-operate with the sponsor and its insurer (or their legal representatives) in their handling thereof.

19 PUBLICATION POLICY

The sponsor shall retain the ownership of all data. When the study is complete the sponsor shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to regulatory authorities. All proposed publications based on this study must be subject to the sponsor's approval requirements.

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalisation of the study report, the results of this study will be submitted for publication and/or posted in a publicly accessible database of clinical trial results.

20 SIGNATURE OF INVESTIGATOR

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

((Type name and job title))	Date (day/month/year)

21 REFERENCE LIST

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22 APPENDICES

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

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"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

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standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

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27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

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publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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The BODE Index

Variable	Points on BODE Index			
	0	1	2	3
FEV1 (% predicted)	≥65	50-64	36-49	≤35
6-Minute Walk Test (meters)	≥350	250-349	150-249	≤149
MMRC Dyspnea Scale	0-1	2	3	4
Body Mass Index	>21	≤21		

Modified Medical Research Council Dyspnoea Scale

Grade

0 "I only get breathless with strenuous exercise"

1 "I get short of breath when hurrying on the level or walking up a slight hill"

2 "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"

3 "I stop for breath after walking about 100 yards or after a few minutes on the level"

4 "I am too breathless to leave the house" or "I am breathless when dressing"

NB: This is the modified MRC scale that uses the same descriptors as the original MRC scale in which the descriptors are numbered 1-5. The modified MRC scale (0-4) is used for calculation of BODE index.

Dennis E. Doherty, MD, FCCP, Mark H. Belfer, DO, FAAFP, Stephen A. Brunton, MD Leonard Fromer, MD, Charlene M. Morris, MPAS, PA-C, Thomas C. Snader, PharmD, CGP, FASCP. Chronic Obstructive Pulmonary Disease: Consensus Recommendations for Early Diagnosis and Treatment. Journal of Family Practice, November, 2006.

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