# Statistical Analysis Plan (SAP)

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| **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 |
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## REVISION HISTORY

| Version/Date | Version name | Section | Changes implemented |
|---|---|---|---|
| Version 1.0/ 07-Sep-2017 | Initial approved version | N/A | N/A |
| Version 2.0/ 16-Nov-2017 | 2.0 | 7.1.4.13 Clinical treatment failure (exploratory composite endpoint)<br><br>7.2 Handling of missing data and outliers | Medical review clarification added.<br><br>A new section for time since last documented COPD exacerbation has been added to define the imputation rules in case of partial date for the last documented COPD exacerbation. |

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# LIST OF ABBREVIATIONS

The following abbreviations will be used within this SAP.

| Abbreviation or special term | Explanation |
|---|---|
| ADaM | Analysis Dataset Model |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALT | Alanine Aminotransferase |
| ANCOVA | Analysis of Covariance |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area Under the Curve |
| BMI | Body Mass Index |
| BODE | Body mass index, airflow Obstruction, Dyspnoea and Exercise index |
| BUN | Blood Urea Nitrogen |
| CDISC | Clinical Data Interchange Standards Consortium |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF | Case Report Form |
| CRQ | Chronic Respiratory Questionnaire |
| CS | Clinically Significant |
| CSR | Clinical Study Report |
| CTF | Clinical Treatment Failure |
| CTMS | Clinical Trial Management System |
| DBL | Database Lock |
| DBP | Diastolic Blood Pressure |
| DMC | Data Monitoring Committee |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EMA | European Medicines Agency |

| | |
|---|---|
| ER | Emergency Room |
| E-R | Exposure-Response |
| 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 |
| ICH | International Conference on Harmonisation |
| ICS | Inhaled Corticosteroid |
| ICU | Intensive Care Unit |
| IL-6 | interleukin-6 |
| IMP | Investigational Medicinal Product |
| INR | International Normalised Ratio |
| IRT | Interactive Response Technology |
| ITT | Intention-To-Treat |
| IV | intravenous |
| kg | Kilogram |
| LABA | Long-Acting β2-Agonist |
| LLOQ | Lower Limit of Quantification |
| LS | Least Square |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| mL | millilitre |
| mMRC | modified Medical Research Council |
| MMRM | Mixed Model for Repeated Measurements |
| MOV | Maximum Observed Value |
| MPO | Myeloperoxidase |

| | |
|---|---|
| NCS | Not Clinically Significant |
| OC | Observed Cases |
| PD | Pharmacodynamic |
| PFT | Pulmonary Function Test |
| PK | Pharmacokinetic |
| PoC | Proof of Concept |
| PP | Per-Protocol |
| PR | Time interval between the onset of the P wave and the beginning of the QRS complex |
| PRO | Patient Reported Outcome |
| PT | Preferred Term |
| QRS | Time interval between the beginning of the Q wave and the termination of the S wave |
| QTc | corrected QT interval of the electrocardiogram |
| QTcB | Bazett-corrected time interval between the Q and T waves |
| QTcF | Fridericia-corrected time interval between the Q and T waves |
| RBC | Red Blood Cell |
| RR | Respiratory Rate |
| SABA | Short-Acting β2-Agonist |
| SAMA | Short-Acting Muscarinic Antagonist |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |
| SDTM | Study Data Tabulation Model |
| SE | Standard Error |
| SI | Standard International |
| SoC | Standard of Care |
| SOC | System Organ Class |
| TEAE | Treatment-Emergent Adverse Event |
| TFLs | Tables, Figures and Listings |
| TNF-α | Tumour Necrosis Factor-alpha |

| | |
|---|---|
| ULN | Upper Limit Normal |
| ULOQ | Upper Limit of Quantification |
| WBC | White Blood Cell |
| WHO | World Health Organisation |
| 6MWT | 6-Minute Walk Test |
| β-HCG | Beta-Human Chorionic Gonadotropin |

# 1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol No. MBCT206: 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.

This analysis plan is based on the final protocol version 1.0 dated 05 November 2015, final protocol version 2.0 (amendment 1) dated 23 December 2015, final protocol version 3.0 (amendment 2) dated 10 March 2016, final protocol version 4.0 (amendment 3) dated 26 May 2016, and final protocol version 5.0 (amendment 4) dated 08 November 2016.

A summary of the key changes to each protocol amendment is presented in Appendix A.

The table of contents and templates for the Tables, Figures and Listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonisation (ICH) E9[1].

All data analyses and generation of TFLs will be performed using SAS 9.4® or higher.

Note: This plan does not address the pharmacokinetic (PK)/pharmacodynamic (PD) analyses of BCT197 (nonlinear mixed effects PK/PD modelling) for this study. These analyses will be detailed in a separate analysis plan and results from the PK/PD modelling will be reported separately from the CSR.

# 2 STUDY OBJECTIVES

## 2.1 Primary objective

The primary objective is 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 one second (FEV1) from baseline (pre-dose) to Day 7.

## 2.2 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:

**Efficacy of BCT197:**

1. Comparison of FEV1 on Days 3, 10, and 14
2. Normalisation evaluation of spirometry parameter (FEV1 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 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) 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 admission until subject is medically ready (COPD-related) for discharge
15. To characterize the 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 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.

## 2.3 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.

# 3 STUDY DESIGN

## 3.1 General study design

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 100 centres in 12 countries (includes Europe [Germany, Italy, UK and some Central and Eastern European countries], Argentina and US). It is planned that approximately 320 subjects will be screened to randomise approximately 270 subjects, and expected that approximately 255 subjects will complete the study and follow-up. Only hospitalised subjects will be recruited.

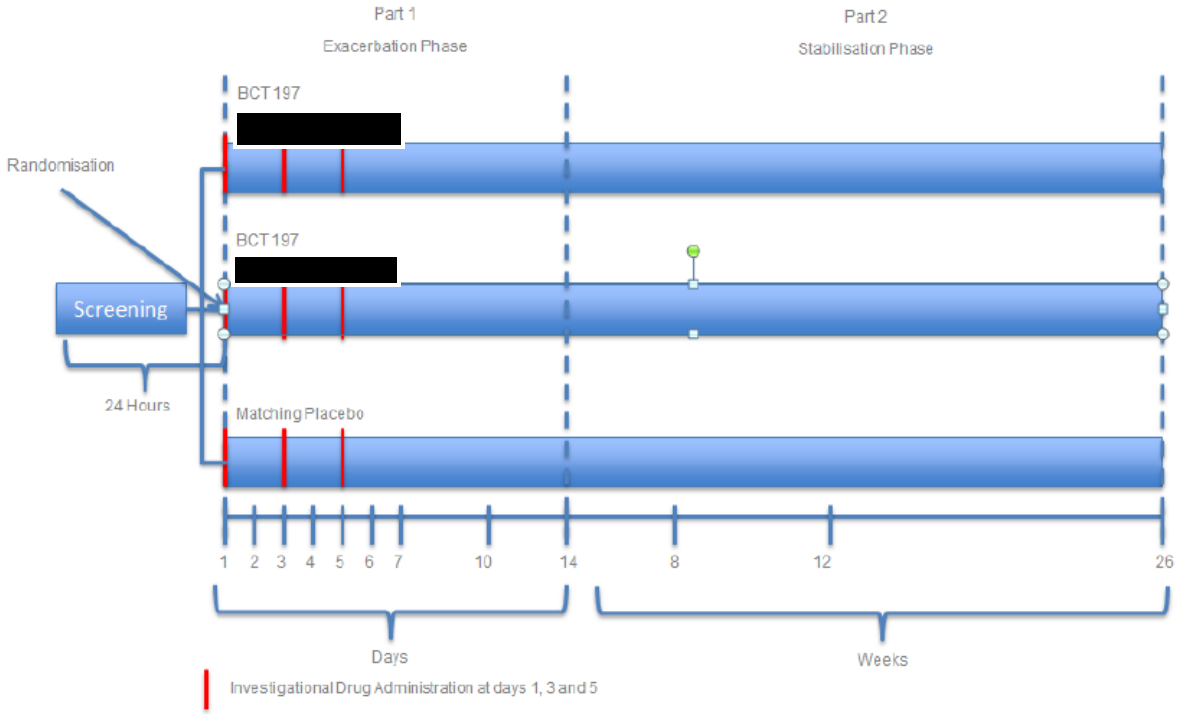
Study is divided into 2 parts:

Acute Exacerbation Phase: from Day 1 (Randomisation day) until Day 14. Drug Administration will be done at days 1, 3 and 5.

Stabilisation Phase: requires subject evaluations at Weeks 8, 12 and 26.

The Study Flow Chart is presented in Figure 1.

**Figure 1: Study Flow Chart**



## 3.2 Randomisation and blinding

### 3.2.1 Randomisation

This is a double-blind and randomised study. Each patient will be randomised in a 1:1:1 ratio to receive 1 of 2 BCT197 treatment schedules or Placebo. At Visit 1 all eligible subjects will be randomised via Interactive Response Technology (IRT) to one of the treatment regimens. The investigator or his/her delegate will contact the IRT after confirming that the subject meets all the inclusion criteria and none of the 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.

### 3.2.2 Blinding

Study Blinding is done 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.

### 3.2.3 Unblinding

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. Unblinding is permissible after database lock or in case of emergency only (with the exception of unblinded DMC staff/members - Refers to SAP Section 8.9 ‘Interim analysis’). Emergency treatment code breaks should only be undertaken when it is essential to treat the subject safely and efficaciously. Emergency code breaks are performed using the IRT.

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

## 3.3 Study treatments and assessments

Study is planned for 26 weeks duration in adult subjects with acute respiratory exacerbations in COPD and divided into two parts: Acute Exacerbation Phase and Stabilisation Phase. All subjects are planned to be treated with test product or placebo on [redacted] after randomisation. Subjects will be screened for up to 24 hours and will be followed daily in the first week, at days 10 and 14, and up to 8, 12 and 26 weeks (+/- 3 days) post-treatment. A total of 12 visits are planned for the two parts of the study.

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 and fulfilling the study entry criteria. 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.

Day 1 to Day 14 – Acute Exacerbation Phase:

Subjects will undergo all safety and efficacy assessments on Day 1. Physical examinations, 12-lead electrocardiograms (ECGs), pulmonary function test (PFT; spirometry), and blood sampling for 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 Days 1-7. 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. The subject should receive a diary on Day 1 after Randomisation to document any occurrences of COPD and rescue medication 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.

[redacted]

Subjects randomised to the placebo arm will be administered two matching placebo capsules that are identical to the test product in appearance but contain no active treatment. The placebo should be taken orally with fluids on days 1, 3 and 5 after randomisation, preferably at the same time each day.

Weeks 8, 12 and 26 – Stabilisation Phase:

Subjects will return to the facility for 3 follow-up visits at Weeks 8, 12 and 26, at which time the required assessments/procedures will be done.

Rescue Medication:

All subjects will be treated as per institution SoC, 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 during the study.

A detailed description of procedures and assessments to be conducted during this study is summarised in the Schedule of Study Assessments in Table 1 below (refers to study protocol Final V5.0).

**Table 1: Schedule of Study 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 $\beta_2$ agonist; SoC: standard of care; 6MWT = 6-minute walking test

# 4 STUDY ENDPOINTS

## 4.1 Primary efficacy endpoint

The primary efficacy endpoint of this study is the change in FEV1 from baseline (pre-dose) to Day 7.

## 4.2 Secondary efficacy endpoints

The secondary efficacy endpoints of this study are:

1. Comparison of FEV1 on Days 3, 10, and 14
2. Normalisation evaluation of spirometry parameter (FEV1 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 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 normalisation 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 admission until the subject is medically ready (COPD-related) for discharge
15. Nonlinear mixed effects pharmacokinetic/pharmacodynamic (PK/PD) models evaluating the relationship between BCT197 exposure and efficacy/safety endpoints.

## 4.3 Exploratory endpoints

The exploratory endpoints of this study are:

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 dyspnoea scale over time
7. BODE index among the three groups at Day 14.

### 4.4 Safety endpoints

The safety endpoints of this study are:

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.

# 5 SAMPLE SIZE AND POWER

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

1. Endpoint: Absolute change in FEV1 (mL) from baseline to Day 7
2. Minimum clinically significant difference between regimens: absolute change of 100 mL
3. Standard deviation (SD) of the difference = 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.

# 6 ANALYSIS POPULATIONS

All primary and secondary efficacy endpoints will be analysed using the intention-to-treat (ITT) population. The Per-Protocol (PP) population will be used for the analysis of the primary endpoint to examine the robustness of the primary analyses. A PP analysis will also be performed on the secondary and exploratory efficacy endpoints for this Proof of Concept (PoC) and hypothesis-generating study.

Safety and tolerability will be analysed using the safety population.

Pharmacokinetic data will be analysed using the PK population.

## 6.1 Intention-To-Treat population (ITT)

The ITT population includes all subjects who:

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

Patients will be included in the analysis per the treatment to which they were randomised.

Note: the 'Baseline' FEV1 value refers to the last non-missing FEV1 value assessed prior to the first dose of study medication.

## 6.2 Safety population (Safety)

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

Patients will be included in the analysis per the treatment actually/1st received.

## 6.3 Per-Protocol population (PP)

The PP population is a subset of the ITT population and includes all randomised subjects who have been treated according to the protocol and fulfil the following criteria (i.e. no major protocol deviations):

- Key inclusion/exclusion criteria met with respect to factors likely to affect the assessment of efficacy in the intended target population
- 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
- Adequate study medication compliance (i.e. full treatment regimen; all 3 doses of study drug received on Days 1, 3, and 5)
- Adequate measurement of the primary variable (i.e. Baseline and Day 7 FEV1 values provided).

Patients will be included in the analysis per the treatment to which they were randomised.

### 6.4 PK population

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

### 6.5 Other Populations Defined for Tables and Listings

For the purposes of tables and listings a further three populations are defined:

- All screened patients
- Screening failure patients
- Randomised population (all randomised patients).

### 6.6 Protocol deviations/violations and exclusions from analysis sets

All violations and exclusions of patients from analysis populations will be finalised at the Classification Meeting prior to the final database lock (DBL)/study unblinding, through clinical review input provided by Mereo, using the following sources of information:

- Supportive patient listings, provided by the ICON lead statistician ahead of the Classification Meeting, based on data recorded on the eCRF.
  The protocol deviations criteria are detailed in Appendix B and specific protocol deviations will be identified by programming.
- Protocol Deviation Logs, retrieved from Clinical Trial Management System (CTMS).

Further, deviations from protocol will be classified as major or minor.

# 7 STATISTICAL CONSIDERATIONS AND ANALYSIS

## 7.1 Derived Variables

### 7.1.1 Study days

Study days will be based on the date of first IMP administration (Study Day 1) and calculated as:

- (assessment date – date of first IMP administration) + 1, for assessments on or after the first IMP administration date
- (assessment date – date of first IMP administration), for assessments prior to first IMP administration date.

### 7.1.2 Follow-up time

Follow-up time (days) will be calculated as:

(date of last contact - date of first IMP administration) + 1

### 7.1.3 Definitions relative to demographic and other baseline characteristics

#### 7.1.3.1 Age

Age at informed consent will be calculated as:
Age (years) = (date of informed consent - date of birth + 1) / 365.25

#### 7.1.3.2 Weight, height and BMI

Weight, recorded in pounds on the eCRF, will be converted in kilograms (1 pound = 0.45359 kg). Height, recorded in inches on the eCRF, will be converted in centimetres (1 inch = 2.54 cm) (International System of Units).

Body mass index (BMI) will be calculated in kg/m2 as: weight (kg)/(height (m))$^2$.

#### 7.1.3.3 Temperature

Temperature, recorded in Fahrenheit degrees on the eCRF, will be converted in Celsius degrees:
Celsius degrees = (Fahrenheit degrees - 32) x (5/9)

#### 7.1.3.4 Smoking duration

Duration of smoking will be calculated in years as:

- Current smoker: (Current Year - Year when subject started smoking) + 1
- Ex-smoker: (Year when subject stopped smoking - Year when subject started smoking) + 1

#### 7.1.3.5 COPD disease duration

Duration of COPD disease will be calculated in years as:

(date of informed consent – date of first diagnosis of COPD + 1) / 365.25

#### 7.1.3.6 Current COPD exacerbation duration

- Duration of current COPD exacerbation symptoms will be calculated in days as:
  (date when symptoms stopped – date when symptoms started + 1)
- Time until complete recovery from the current COPD exacerbation will be calculated in days as:
  (date when patient achieved complete recovery from the current exacerbation – date when symptoms started).

Where 'Date when symptoms started', 'Date when symptoms stopped', and 'Date when patient achieved complete recovery from the current exacerbation' are recorded on the 'Current COPD Exacerbation' form of the eCRF.

#### 7.1.3.7 Times from start/stop of current COPD exacerbation to first dosing

Times from start/stop of current COPD exacerbation symptoms to first dose of study medication will be calculated in days as:
(date of first study treatment dose – date when symptoms started/stopped).

#### 7.1.3.8 Time since last documented COPD exacerbation

Time since last documented COPD exacerbation will be calculated in months as:

(date of informed consent – date of last documented COPD exacerbation + 1) / 30.4375

### 7.1.4 Definitions relative to efficacy criteria

#### 7.1.4.1 COPD exacerbation (moderate and severe)

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.

#### 7.1.4.2 FEV1 normalisation

FEV1 normalisation is achieved if FEV1 returns to a value ≥ 89%[3] of the most recent FEV1 value measured within the last 12 months outside an exacerbation (pre-study FEV1 value).

#### 7.1.4.3 FEV1/FVC normalisation

FEV1/FVC normalisation is achieved if FEV1/FVC returns to a value ≥ 89%[3] of the most recent FEV1/FVC value measured within the last 12 months outside an exacerbation (pre-study FEV1/FVC value).

#### 7.1.4.4 Time to improvement in FEV1 value

##### 7.1.4.4.1 Time to improvement of 100 mL in FEV1

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

Change in FEV1 = FEV1 value (time T) – FEV1 value (baseline).

**Table 2-1: Criteria for event/censored for assessment of Time to improvement of 100 mL (FEV1)**

| Situation | Date of event or Censoring | Time to improvement of 100 mL | Outcome |
|---|---|---|---|
| Subjects who meet criteria of change in FEV1 ≥ + 100 mL | Date when the criteria is met | Time from initiation of study treatment until Date when the aforesaid criteria is met | Event |
| Subjects who never meet change in FEV1 ≥ + 100 mL | Date of the last evaluable spirometry | Time from initiation of study treatment until Date of the last evaluable spirometry | Censored |
| Subjects who died | Death date | Time from initiation of study treatment until Date of death | Censored |
| Subjects who withdrew or were lost to follow-up during the study | Withdrawal or last contact date | Time from initiation of study treatment until Date of withdrawal or last contact date | Censored |

##### 7.1.4.4.2 Time to improvement of 80 mL in FEV1

This is defined as the time (in days) from initiation of study treatment until the change in FEV1 is ≥ + 80 mL (improvement).

Change in FEV1 = FEV1 value (time T) – FEV1 value (baseline).

**Table 2-2: Criteria for event/censored for assessment of Time to improvement of 80 mL (FEV1)**

| Situation | Date of event or Censoring | Time to improvement of 80 mL | Outcome |
|---|---|---|---|
| Subjects who meet criteria of change in FEV1 ≥ + 80 mL | Date when the criteria is met | Time from initiation of study treatment until Date when the aforesaid criteria is met | Event |
| Subjects who never meet change in FEV1 ≥ + 80 mL | Date of the last evaluable spirometry | Time from initiation of study treatment until Date of the last evaluable spirometry | Censored |
| Subjects who died | Death date | Time from initiation of study treatment until Date of death | Censored |
| Subjects who withdrew or were lost to follow-up during the study | Withdrawal or last contact date | Time from initiation of study treatment until Date of withdrawal or last contact date | Censored |

#### 7.1.4.5 Standardised Area Under Curve (AUC) of FEV1

AUC will be calculated according to the trapezoidal rule. The trapezoidal rule is a numerical method to be used to approximate the integral or the area under a curve. Using trapezoidal rule to approximate the area under a curve first involves dividing the area into a number of strips of equal width. Then, approximating the area of each strip by the area of the trapezium formed when the upper end is replaced by a chord. The sum of these approximations gives the final numerical result of the area under the curve.

The (standardised) AUC of the FEV1 will be calculated from Day (a) to Day (b) using the trapezoidal rule as follows:

$$AUC(a,b) = \left( \sum_{x=a+1}^{b} \frac{(Y_{x-1} + Y_x)(x-(x-1))}{2} \right) \left( \frac{1}{b-a} \right)$$

where x = Actual day of measurement and $Y_x$ = FEV1 value at Day x

Missing values for the calculation of FEV1 AUC will be handled as follows:

- If single or more intermediate values are missing between two non-missing values, they will be ignored and the component of the AUC will be calculated between 2 days for this part of the curve.
- If FEV1 value at Day 1 pre-dose (baseline) is missing then the AUC will be missing.

- For the Day 1 – 3 AUC, Day 1 – 7 AUC, Day 1 – 10 AUC and Day 1 – 14 AUC: if < 50% of values are available from Day 1 pre-dose (baseline), then the AUC will be set as missing.

#### 7.1.4.6 Respiratory Rate (RR) normalisation

RR is normalised if RR returns to a baseline plateau level achieved after the acute COPD exacerbation during the Stabilisation Phase. This baseline plateau value is defined on a patient basis, and corresponds to the mean of the 3 RR values recorded during the Stabilisation Phase for each patient (mean of RR at Weeks 8, 12 and 26). Only 1 of the 3 data points needs to be present for this computation. In the case that all three RR values are missing during the Stabilisation Phase for a patient, the baseline plateau value will be set to 20 breaths/min[2].

To summarise, RR is normalised if RR returns to a value ≤ P breaths/min; where P ("Plateau") equals to:

- mean of RR at Weeks 8, 12 and 26 (on a patient basis)
- 20 breaths/min, if all three RR values at Weeks 8, 12 and 26 are missing.

#### 7.1.4.7 Questionnaire EXACT-PRO

The EXACT is a 14-item patient reported outcome (PRO) daily diary used to quantify and measure exacerbations of COPD (Mackay 2014[4]). 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 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.

<u>EXACT Total Score</u>

An EXACT Total score is computed for each day of diary collection. The EXACT Total score is based on a logit scoring system with conversion to a 0 to 100 scale for ease of interpretation and use. The total score is used in the determination of exacerbation frequency, severity and duration of exacerbation. Specifically, changes in the total score are used to define onset and recovery from an exacerbation event and the magnitude of that event.

EXACT Domain Scores

Additional information regarding the patient's condition can be obtained through 3 domain scores embedded within the EXACT measure: Breathlessness, Cough & Sputum, and Chest Symptoms. These scores also range from 0 to 100 with higher scores indicating more severe symptoms.

Appendix C describes the EXACT raw scores and EXACT scoring instructions to compute the EXACT daily scores and event frequency, duration and severity.

#### 7.1.4.8 Time to improvement/recovery based on EXACT-PRO total score

**Table 3: Criteria for event/censored for assessment of Time to improvement/recovery (EXACT-PRO)**

| Situation | Date of event or Censoring | Time to improvement/recovery (EXACT-PRO) | Outcome |
|---|---|---|---|
| Subjects who had current COPD exacerbation improved/recovered over the observed period | Date of improvement/ recovery of current COPD exacerbation | Time from initiation of study treatment until Date of improvement/recovery of current COPD exacerbation | Event |
| Subjects who never had current COPD exacerbation improved/recovered over the observed period | Date of the last evaluable EXACT-PRO assessment | Time from initiation of study treatment until Date of the last evaluable EXACT-PRO assessment | Censored |
| Subjects who died over the observed period | Death date | Time from initiation of study treatment until Date of death | Censored |
| Subjects who withdrew or were lost to follow-up over the observed period | Withdrawal or last contact date | Time from initiation of study treatment until Date of withdrawal or last contact date | Censored |

#### 7.1.4.9 Standardised AUC of EXACT-PRO Total Score

The (standardized) AUC of the EXACT-PRO will be calculated from Day (a) to Day (b) using the trapezoidal rule as follows:

$$AUC(a,b) = \left( \sum_{X=a+1}^{b} \frac{(Y_{x-1} + Y_x)(x-(x-1))}{2} \right) \left( \frac{1}{b-a} \right)$$

where $x$ = Actual day of measurement and $Y_x$ = Rolling average at Day $x$.

AUCs for EXACT-PRO subscores will also be calculated.

Missing values for the calculation of EXACT-PRO score and subscores AUCs will be handled as follows:

- If single or more intermediate value is missing between two non-missing values, they will be ignored and the component of the AUC will be calculated between 2 days for this part of the curve.
- If baseline EXACT-PRO rolling average (i.e. EXACT-PRO score at Day 1) is missing then the AUC will be missing.
- For the Day 1 – 3 AUC:
    - if < 50% of rolling average values are available from Day 1, then the AUC will be set as missing.
    - if the rolling average is missing at Day 3 then the average between the Rolling Average at Day 2 and the Rolling Average at Day 4 will be used in the AUC calculation in place of the Rolling Average at Day 3.
- For the Day 1 – 5 AUC:
    - if < 50% of rolling average values are available from Day 1, then the AUC will be set as missing.
    - if the rolling average is missing at Day 5 then the average between the Rolling Average at Day 4 and the Rolling Average at Day 6 will be used in the AUC calculation in place of the Rolling Average at Day 5.
- For the Day 1 – 7 AUC:
    - if < 50% of rolling average values are available from Day 1, then the AUC will be set as missing.
    - if the rolling average is missing at Day 7 then the average between the Rolling Average at Day 6 and the Rolling Average at Day 8 will be used in the AUC calculation in place of the Rolling Average at Day 7.
- For the Day 1 – 10 AUC:
    - if < 50% of rolling average values are available from Day 1, then the AUC will be set as missing.
    - if the rolling average is missing at Day 10 then the average between the Rolling Average at Day 9 and the Rolling Average at Day 11 will be used in the AUC calculation in place of the Rolling Average at Day 10.
- For the Day 1 – 14 AUC:
    - if < 50% of rolling average values are available from Day 1, then the AUC will be set as missing.
    - if the rolling average is missing at Day 14 then the average between the Rolling Average at Day 13 and the Rolling Average at Day 15 will be used in the AUC calculation in place of the Rolling Average at Day 14.

- For the Day 1 – 29 AUC:
    - if the rolling average is missing at Day 29 no further imputation will be performed and the Day 29 will be considered missing in the calculation of the AUC.

#### 7.1.4.10 Time to next COPD exacerbation

The time to next COPD exacerbation (in days) is defined as:

(Date when first COPD exacerbation symptoms started – Date when current COPD exacerbation symptoms stopped),

where COPD exacerbations experienced during the study are recorded on the 'Acute Exacerbation COPD' form of the eCRF, i.e.:

- Start date of COPD exacerbation is the 'date when symptoms started' recorded on the form
- COPD exacerbation has an intensity recorded as 'Mild', 'Moderate' or 'Severe' on the form.

**Table 4: Criteria for event/censored for assessment of Time to next COPD exacerbation**

| Situation | Date of event or Censoring | Time to next COPD exacerbation | Outcome |
|---|---|---|---|
| Subjects who had next COPD exacerbation | Date of next COPD exacerbation after entering in study | Time from when current COPD exacerbation symptoms stopped until Date of next COPD exacerbation after entering in study | Event |
| Subjects who never had COPD exacerbation in study period | Withdrawal or last contact date | Time from when current COPD exacerbation symptoms stopped until Date of withdrawal or last contact date | Censored |
| Subjects who died | Death date | Time from when current COPD exacerbation symptoms stopped until Date of death | Censored |
| Subjects who withdrew or were lost to follow-up during the study | Withdrawal or last contact date | Time from when current COPD exacerbation symptoms stopped until Date of withdrawal or last contact date | Censored |

#### 7.1.4.11 Time from hospitalisation admission until subject is medically ready for discharge (current COPD)

This time (in days) will be calculated as:

(Date subject is medically ready for discharge from hospital – Date of hospitalisation admission),

where 'Date of hospitalisation admission' and 'Date subject is medically ready for discharge from hospital' are recorded on the 'Current COPD Exacerbation' form of the eCRF.

**Table 5: Criteria for event/censored for assessment of Time from hospitalisation admission until subject is medically ready for discharge (current COPD)**

| Situation | Date of event or Censoring | Time from hospitalisation admission until subject is medically ready for discharge | Outcome |
|---|---|---|---|
| Subjects who were medically ready for discharge from hospital | Date subject is medically ready for discharge | Time from hospitalisation admission until Time subject is medically ready for discharge | Event |
| Subjects who were not medically ready for discharge from hospital | Withdrawal or last contact date | Time from hospitalisation admission until Date of withdrawal or last contact date | Censored |
| Subjects who died | Death date | Time from hospitalisation admission until Date of death | Censored |
| Subjects who withdrew or were lost to follow-up during the study | Withdrawal or last contact date | Time from hospitalisation admission until Date of withdrawal or last contact date | Censored |

#### 7.1.4.12 Percentage of days with intake of COPD rescue therapy

Patients will complete the EXACT-PRO starting from Study Day 1 and will record rescue medication use and any occurrences of COPD once a day (evening) in the diary. The percentage of days with intake of rescue medications will be evaluated on the basis of the information recorded daily by the patient on the diaries.

A day will be considered with intake of rescue medications if the answer to the question "How many puffs of rescue medication did you take since last evening?" is > 0.

**Inter-Visit Period:**

For the calculation of the percentage of days, the inter-visit periods are defined as below:

| Inter-visit period visit i - visit i+1 ($1 \leq i \leq 11$) | |
|---|---|
| Date of start of the period | Date of end the period |
| • If i=1 then date of start = date of Study Day 1.<br>• Else date of start = date of visit i. | • If visit i is NOT the last clinic visit performed before the End of Study then date of end = date of visit i+1 – 1 day (i.e., the day before visit i+1).<br>• Else date of end = date of End of Study. This includes the case date of visit i+1 = date of End of Study. |

On a per patient basis, the percentage of days in each inter-visit period will be calculated using the following formula:

- % of days with rescue medication (inter-visit period) = (Number of days with rescue medication during the inter-visit period / Number of days with data recorded during the inter-visit period)*100.

**Acute Exacerbation Phase:**

- Percentage of days: data recorded from Study Day 1 to the day before Visit 9/Day 14 will be considered as data of the Acute Exacerbation Phase.

On a per patient basis, the percentage of days in the Acute Exacerbation Phase will be calculated using the following formula:

- % of days with rescue medication (Acute Exacerbation Phase) = (Number of days with rescue medication during the Acute Exacerbation Phase/Number of days with data recorded during the Acute Exacerbation Phase)*100.

**Stabilisation Phase:**

- Percentage of days: data recorded from the day of Visit 9/Day 14 to the day of End of Study will be considered as data of the Stabilisation Phase.

On a per patient basis, the percentage of days in the Stabilisation Phase will be calculated using the following formula:

- % of days with rescue medication (Stabilisation Phase) = (Number of days with rescue medication during the Stabilisation Phase/Number of days with data recorded during the Stabilisation Phase)*100.

#### 7.1.4.13 Clinical treatment failure (exploratory composite endpoint)

Clinical treatment failure (CTF) is defined as a composite endpoint in which a patient meets any one of the following criteria (a medical review will be also performed to review each patient meeting these criteria because these selections can select non-CTF patients):

- Worsening of symptoms warranting the addition of another antibiotic or initiation of a new

antibiotic (Criterion 1)
- Worsening of symptoms warranting an increase in dose of oral corticosteroids or initiation of new oral corticosteroids (Criterion 2)
- Worsening of symptoms requiring additional treatment regimen of oral corticosteroids and/or antibiotics after completion of the initial regimen (Criterion 3)
- Re-hospitalisation due to worsening of COPD and requiring additional treatment during the duration of the study due to an exacerbation of respiratory symptoms (emergency room admission for longer than 24 hours will qualify as a hospitalisation) (Criterion 4)
- COPD-related death (Criterion 5).

Criterion 1: Worsening of symptoms warranting the addition of another antibiotic or initiation of a new antibiotic will be derived from the 'Prior (Last 6 months medication) and Concomitant Medication' form of the eCRF. The medications recorded on this form to be considered for this criterion will verify:

- Antibiotics: Anatomical Therapeutic Chemical (ATC) code 'J01'
- Medication administered for COPD exacerbations only, i.e. with indication = 'COPD exacerbation: current/during the study'
- Medication started after Study Day 1 (i.e. ≥ Randomisation date + 1) and prior to or on completion of the initial treatment (systemic corticosteroids or antibiotics) for the current COPD exacerbation (started no longer than 24 hours before randomisation).

Criterion 2: Worsening of symptoms warranting an increase in dose of oral corticosteroids or initiation of new oral corticosteroids will be derived from the 'Prior (Last 6 months medication) and Concomitant Medication' form of the eCRF. The medications recorded on this form to be considered for this criterion will verify:

- Systemic corticosteroids: ATC code 'H02'
- Route 'PO = oral'
- Medication administered for COPD exacerbations only, i.e. with indication = 'COPD exacerbation: current/during the study'
- Medication started after Study Day 1 (i.e. ≥ Randomisation date + 1) and prior to or on completion of the initial treatment (systemic corticosteroids or antibiotics) for the current COPD exacerbation (started no longer than 24 hours before randomisation).

Criterion 3: Worsening of symptoms requiring additional treatment regimen of oral corticosteroids and/or antibiotics after completion of the initial regimen will be derived from the 'Prior (Last 6 months medication) and Concomitant Medication' form of the eCRF. The medications recorded on this form to be considered for this criterion will verify:

- Systemic oral corticosteroids (ATC code 'H02' and Route 'PO = oral') or Antibiotics (ATC code 'J01')
- Medication administered for COPD exacerbations only, i.e. with indication = 'COPD

exacerbation: current/during the study'

- Medication started after completion of the initial treatment (systemic corticosteroids or antibiotics) for the current COPD exacerbation (started no longer than 24 hours before randomisation).

Criterion 4: Re-hospitalisation due to worsening of COPD and requiring additional treatment during the duration of the study due to an exacerbation of respiratory symptoms will be determined based on the COPD exacerbations experienced after the initial study COPD exacerbation and recorded on the 'Acute Exacerbation COPD' form of the eCRF. This criterion will verify:

- "Has the patient experienced any COPD exacerbations after the initial qualifying study exacerbation subsided?" = 'Yes'
- Treatment: Systemic corticosteroids = 'Yes' or Antibiotics = 'Yes'
- Hospitalisation = 'Yes' or (Emergency room = 'Yes' with admission longer than 24 hours).

Criterion 5: COPD-related death will be determined based on the COPD exacerbations experienced during the study (including the initial study COPD exacerbation) and recorded on the 'Adverse Event' form of the eCRF. This criterion will verify:

- AE Preferred Term 'Chronic obstructive pulmonary disease'
- Serious AE that 'Results in death'.

The cumulative incidence of CTF as well as each of the individual criteria will be evaluated at Day 30, Day 60, Day 90, Day 120, Day 150 and Day 180.

#### 7.1.4.14 Time to clinical treatment failure

The time to clinical treatment failure (in days) is defined as:

(Date when any one of the criteria defining the composite endpoint occurred for the first time – Date of initiation of study treatment),

where acute COPD exacerbations experienced during the study and their characteristics are recorded on the 'Acute Exacerbation COPD' form of the eCRF, i.e. in particular:

- Date of first antibiotic intake and/or first systemic corticosteroid intake for treating the COPD exacerbation
- Date of hospitalisation admission for the COPD exacerbation
- Date of emergency room admission (emergency room admission for longer than 24 hours will qualify as a hospitalisation) for the COPD exacerbation
- Date the COPD exacerbation (assessed as an AE) results in death.

**Table 6: Criteria for event/censored for assessment of Time to clinical treatment failure**

| Situation | Date of event or Censoring | Time to clinical treatment failure | Outcome |
|---|---|---|---|
| Subjects who had any one of the criteria defining the composite endpoint | Date of clinical treatment failure after entering in study | (Time from initiation of study treatment until Date of clinical treatment failure after entering in study) | Event |
| Subjects who never had any one of the criteria defining the composite endpoint in study period | Withdrawal or last contact date | (Time from initiation of study treatment until Date of withdrawal or last contact date) | Censored |
| Subjects who died (not COPD-related) | Death date | (Time from initiation of study treatment until Date of death) | Censored |
| Subjects who withdrew or were lost to follow-up during the study | Withdrawal or last contact date | (Time from initiation of study treatment until Date of withdrawal or last contact date) | Censored |

#### 7.1.4.15 Chronic Respiratory Questionnaire (CRQ)

The CRQ is an instrument developed to measure quality of life of patients with COPD. The CRQ contains 20 questions which can be divided into four domains: dyspnoea (5 questions), fatigue (4 questions), emotional function (7 questions) and mastery (4 questions; the subject's feeling of control over their disease). The dyspnoea component is "individualised" (not standardised) which means that it is made up of five activities chosen by a patient to cause the greatest shortness of breath. The patient then rates the dyspnoea on these 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. 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 ranging from 1 (maximum impairment) to 7 (no impairment). The results are expressed as the mean score for each domain (i.e. the total score per domain divided by the corresponding number of items) and the mean total score (i.e. the mean of the scores from the 3 domains fatigue, emotional function and mastery). (Refer Appendix D).

The four domain scores will be calculated based on:

- Dyspnoea from questions 1, 2, 3, 4, 5
- Fatigue from questions 8, 11, 15, 17
- Emotional function from questions 6, 9, 12, 14, 16, 18, 20

- Mastery from questions 7, 10, 13, 19.

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.

#### 7.1.4.16 Cumulative oral/IV steroid dose

The cumulative oral/IV steroid dose during the duration of current COPD exacerbation will be derived on a patient level from the 'Prior (Last 6 months medication) and Concomitant Medication' form of the eCRF. The medications recorded on this form to be considered for this exploratory endpoint will verify:

- Systemic corticosteroids: ATC code 'H02'
- Route 'IV = intravenous' or 'PO = oral'
- Medication administered for COPD exacerbations only (i.e. with indication = 'COPD exacerbation: current/during the study') and taken during the duration of current COPD exacerbation (i.e. from the date when symptoms started until the date when symptoms stopped).

Moreover, the dose of treatment recorded on the form for selected systemic corticosteroids will be converted to 'mg', in case the unit recorded on the form is not 'mg'.

Then a correction factor will apply on the oral/IV steroid dosages (mg) using dosing equivalencies, i.e.:

- 1 mg of betamethasone = +/- 7 mg of prednisone equivalence
- 1 mg of cortisone = +/- 0.2 mg of prednisone equivalence
- 1 mg of dexamethasone = +/- 7 mg of prednisone equivalence
- 1 mg of hydrocortisone = +/- 0.25 mg of prednisone equivalence
- 1 mg of methylprednisolone = +/- 1 mg of prednisone equivalence
- 1 mg of prednisolone = +/- 1 mg of prednisone equivalence
- 1 mg of triamcinolone = +/- 1 mg of prednisone equivalence.

Finally, the cumulative oral/IV steroid dose (prednisone equivalent dose) per patient will be calculated as the sum of all prednisone equivalent doses taken by the patient each day during the duration of current COPD exacerbation.

#### 7.1.4.17 BODE index

**BMI**

The BMI is to be calculated from the weight and height obtained at scheduled visits where the BODE index is required. BODE uses the binary classification for BMI > 21 kg/m$^2$ (scored as 0) or ≤ 21 kg/m$^2$ (scored as 1).

**Obstruction**

The level of obstruction for the BODE index will be collected from the spirometry done at the

timepoints where the BODE index is specified. The index to be used is the FEV1 (% predicted value). BODE uses the following classification for FEV1 (% predicted): ≥ 65% (scored as 0), 50-64% (scored as 1), 36-49 % (scored as 2) or ≤ 35% (scored as 3).

**Dyspnoea (mMRC score)**

The mMRC dyspnoea scale is a questionnaire that consists of five statements about perceived breathlessness: grade 0 (scored as 0), "I only get breathless with strenuous exercise"; grade 1 (scored as 0), "I get short of breath when hurrying on the level or up a slight hill"; grade 2 (scored as 1), "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 (scored as 2), "I stop for breath after walking 100 yards or after a few minutes on the level"; grade 4 (scored as 3), "I am too breathless to leave the house".

**Exercise (6MWT)**

The 6-Minute Walk Test (6MWT) to achieve the BODE index will be performed at scheduled visits 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.

The distance covered over 6 minutes will be recorded as well as the speed (if available) and the oxygen saturation. BODE uses the following classification for 6MWT (meters): ≥ 350 meters (scored as 0), 250-349 meters (scored as 1), 150-249 meters (scored as 2), ≤ 149 meters (scored as 3) or Not Done (scored as 3).

**BODE Index**

The BODE index is used to evaluate the functional status of subjects with COPD. Each parameter of the index (airflow obstruction, dyspnoea score per mMRC and exercise tolerance using the 6MWT) is graded from 0 to 3 with the exception of BMI which is graded as 0 or 1. The overall BODE score is the sum of all 4 individual scores and may vary from 0 to 10. (Refer Appendix E)

### 7.1.5 Definitions relative to safety parameters

#### 7.1.5.1 Adverse Event (AE)

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.

#### 7.1.5.2 Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is defined as an AE that results in one of the following outcomes:

- Results in death
- Is life-threatening
- Requires in-patient hospitalisation or prolongs existing hospitalisation (this does not include prolonged hospitalisation for study purposes)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event.

#### 7.1.5.3 Duration of AEs

The duration of an AE will be calculated as the resolution date minus the date at which it first appeared plus 1.

In the case of an AE still continuing at the end of the study, the duration will be considered as unknown.

#### 7.1.5.4 Relationship of AEs

The relationship between an AE and the study treatment (BCT197 or placebo) will be determined by the Investigator on the basis of his or her clinical judgment and the definitions in Table 7.

**Table 7: Assessment of Relationship**

| | |
|---|---|
| Reasonable possibility of relatedness | If there is enough evidence or argument to suggest the causal relationship. The investigator should consider, but not limited to, before reaching up to a decision on causality assessment:<br>o Time relationship between study drug intake and event's onset<br>o Dechallenge<br>o Rechallenge<br>o Medical History<br>o Study treatment<br>o Mechanism of action of study drug<br>o Class effect<br>o Concomitant treatments in use<br>o Withdrawal of study treatment<br>o Lack of efficacy/worsening of existing condition<br>o Erroneous treatment with study medication or concomitant medication<br>o Protocol related process. |
| No reasonable possibility of relatedness | o there are NOT enough evidence or argument to suggest the causal relationship |

Adverse events will be considered causally related to the use of the IMP when the relationship is

not recorded. For pre-treatment adverse events, a causality assessment is not relevant.

#### 7.1.5.5 Intensity of AEs

The Investigator will assess the intensity of AEs using the following definitions:

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

#### 7.1.5.6 Adverse Event of Special Interest (AESI)

Following Adverse Events are of Special Interest:

- Pneumonia
- Liver injury (liver enzymes: ALT, AST, bilirubin total and fractions)
- Dermatologic events (Rash/Acneiform dermatitis/Pruritus)
- Headache
- Inflammation of cervix and vagina.

## 7.2 Handling of missing data and outliers

### 7.2.1 Missing data analysis methods

No strategy for imputation of missing values from subjects who dropped out will be applied because the mixed model for repeated measurements analysis done for the primary endpoint is known to produce a valid analysis if the drop-out mechanism is missing at random[5].

The analysis (and clinical database) will only include those FEV1 results assessed as being of acceptable quality for each time point.

### 7.2.2 Handling of missing or incomplete dates

#### 7.2.2.1 Partial dates of first COPD diagnosis

In order to calculate the COPD disease duration (i.e. time since first COPD diagnosis), the following rules will be applied for partial dates for first diagnosis of COPD:

- if the day of the month is missing it is imputed to be the 15$^{th}$
- if both the day and month are missing, they are imputed to be June 30
- missing years will be left as missing.

The above will be flagged and described as a footnote in the appropriate listings.

#### 7.2.2.2 Partial dates of current COPD exacerbation symptoms start/stop

In order to calculate the current COPD exacerbation duration (i.e. from the date when symptoms started until the date when symptoms stopped) and the times from start/stop of current COPD exacerbation to first dosing, the following rules will be applied for partial dates for current COPD exacerbation symptoms start and stop:

- if the day of the month is missing it is imputed to be the 15th
- missing months will be left as missing
- missing years will be left as missing.

The above will be flagged and described as a footnote in the appropriate listings.

#### 7.2.2.3 Concomitant medications definitions and handling of missing or incomplete dates

Medications will be assigned as being prior to study treatment, concomitant with study treatment, or occurring in the Stabilisation Phase, based on the start and stop dates of the medication and the IMP dosing.

If the medication stop date is before the date of the first IMP dose, the medication will be assigned as being discontinued prior to study treatment. Otherwise, the medication will be assigned as being concomitant with study treatment unless the start date of the medication is after Visit 9 date, when it will then be classified as occurring in the post-treatment period.

Should the stop date for a medication be missing (not ongoing) or incomplete to the extent that it could be before, on or after the time of start of study treatment, then it will be assumed that the medication was stopped on or after the start of study treatment (i.e. reported as concomitant medication). Similarly, if it is not clear whether the medication start date was on or before, or after the Visit 9 date, then it will be assumed the medication was begun on or before the Visit 9 date (i.e. reported as a concomitant medication) (worst case approach).

For listings of medications, dates will be presented as they have been recorded (missing and partial dates will not be replaced).

#### 7.2.2.4 Definition of treatment-emergent AEs and handling of missing or incomplete dates

A Treatment-Emergent AE (TEAE) is defined as an AE occurring or worsening on or after the first IMP dose. Events with an onset date at or after the patient has signed the ICF and prior to the first IMP dose will be classified as pre-treatment AEs.

In the event of an incomplete onset date, the event will be considered to be treatment-emergent unless the partial onset date information or complete or partial end date confirms onset or end prior to the first IMP dose date (worst case approach).

Analysis of TEAEs/SAEs will be performed separately for Acute Exacerbation Phase (from Study Day 1 until Day 14 included) and Stabilisation Phase (after Day 14 until Week 26), as well as overall (both study phases combined together). Events with an onset date after the date of Visit 9 (Day 14) will be classified as occurring during the Stabilisation Phase.

Should any onset date for a TEAE be incomplete then it will be assumed that the TEAE occurred during the Acute Exacerbation Phase, unless the partial onset date information confirms onset after

the Visit 9 date (worst case approach).

In case of partial onset date of COPD exacerbation reported in the 'Acute Exacerbation COPD' form of the eCRF, the onset of the event will be assumed as the first day of the month in the analysis of time to next COPD exacerbation.

For AEs listings, dates will be presented as they have been recorded (missing and partial dates will not be replaced).

#### 7.2.2.5 Time since last documented COPD exacerbation

In order to calculate the time since last documented COPD exacerbation, the following rule will be applied for partial dates for last documented COPD exacerbation:

- if the day of the month is missing it is imputed to be the last day of the month.

The above will be flagged and described as a footnote in the appropriate listings.

### 7.2.3 Missing items in a questionnaire (CRQ) within a patient/visit

The method of data imputation to be used for CRQ is to substitute a person-specific estimate for any missing item, when the respondent answered at least 50% of the items in a scale or subscale. The estimate is the average score, across completed items in the same scale or subscale, for that respondent. Otherwise the average score will be set to missing for that patient/visit.

### 7.2.4 Handling of changes in study endpoints due to protocol amendments

The Appendix A summarises the key changes to each protocol amendment and which study endpoints are impacted by the protocol amendments.

Sensitivity and subgroup analyses will be performed on the study endpoints impacted by the protocol amendments, and are detailed throughout this SAP when applicable.

# 8 STATISTICAL METHODS

## 8.1 General statistical conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

### 8.1.1 Populations for analysis

Demographic and baseline characteristics will be summarised in the Safety, ITT and PP populations, unless otherwise stated.

Analyses of the primary efficacy endpoint will be performed on the ITT population, and also on the PP population as a sensitivity analysis.

The secondary and exploratory efficacy endpoints will be analysed using the ITT and PP populations for this PoC and hypothesis-generating study.

The safety and tolerability variables will be analysed using the Safety population.

PK data will be analysed using the PK population.

For the populations to be considered in the subgroup analyses, see section 8.8.3 below.

### 8.1.2 Treatment groups

Statistics will be displayed for the following treatment groups:

[redacted]

### 8.1.3 Descriptive statistics

Continuous variables will be summarised using descriptive statistics including number of non-missing observations (n), arithmetic mean (Mean), median (Median), standard deviation (SD), minimum value (Min) and maximum value (Max). One additional decimal point for mean and median and 2 additional decimal points for SD will be used.

For categorical variables, summaries will include the number of non-missing observations (n) or the number of patients in the population (N) as applicable, the counts of subjects and percentages. Percentages will be rounded to one decimal place. The number of missing values will be presented as a separate category with no percentage, but only if any missing value is recorded in the data for that summary.

For efficacy and safety data, summary statistics will be presented at each visit when relevant. Changes from baseline will be summarised in a similar manner.

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

### 8.1.4 Statistical significance

Unless otherwise stated, all statistical testing will be two-sided and conducted at the significance (alpha) level of 0.05. Two-sided 95% confidence intervals (CIs) will be provided when relevant. All three treatment regimens will be assessed by pairwise comparisons for efficacy data, and no adjustment for multiplicity will be made.

### 8.1.5 Definitions of Baseline

The efficacy/exploratory endpoints to be analysed separately during the Acute Exacerbation Phase and the Stabilisation Phase are the EXACT-PRO total score and subscores (and exacerbation parameters derived from EXACT-PRO), the change from baseline in CRQ over time and the change from baseline in mMRC dyspnoea scale over time.

For summary purposes, the baseline value for Acute Exacerbation Phase will be defined as the last non-missing value collected prior to the first dose of study medication, unless other specified. Moreover, for the efficacy/exploratory endpoints to be analysed separately during the Acute Exacerbation Phase (from Study Day 1 until Day 14) and the Stabilisation Phase (from Day 14 until Week 26), the baseline value for Stabilisation Phase will be defined as the value collected on Visit 9 (Day 14), unless other specified. For Stabilisation Phase, no value available prior to Visit 9 (Day 14) will be used for definition of baseline, as the patient might not yet be under stable condition for COPD prior to Day 14.

For EXACT-PRO, as there is no stable period during which EXACT-PRO scores are collected prior to administrating the study drug, the definition of the Baseline EXACT-PRO from the user manual[6] will not be used for Acute Exacerbation Phase. The score and subscores obtained on Day 1 of the EXACT-PRO observation period, which corresponds to Study Day 1, will be used as the baseline for Acute Exacerbation Phase. Moreover, the Baseline EXACT-PRO score (or subscores) for Stabilisation Phase will be defined as the mean EXACT score during the first 7 days of the Stabilisation Phase (Week 3; Days 15-21), with a minimum of 4 days of available data required to compute the baseline value. If 4 or more of the first 7 days of data are not available, the baseline EXACT-PRO score for Stabilisation Phase will not be calculated.

### 8.1.6 Visit dates

For each visit, the date recorded by the Investigator in the eCRF (variable SVSTDTC in the SDTM SV dataset) will be considered as the visit date in all the algorithms and the listings.

### 8.1.7 Data re-allocation

The following general rules to handle repeated assessments will be considered:

- PFT (spirometry):
  - If the spirometry was repeated before the first study medication intake, the last assessment performed will be considered as the Visit 1 assessment in all the analyses.
  - If the spirometry was repeated at a visit after the first study medication intake, the assessment performed 'post-bronchodilator' will be considered as the visit assessment in all the analyses.
- 12-lead ECG:
  - in case of multiple measurements associated to the same timepoint (e.g. triplicate ECGs), the average value will be considered for HR, RR interval, PR interval, QRS duration, QT interval, QTcB interval and QTcF interval.
  - The last 12-lead ECG performed before the first study medication intake will be considered in the analysis as the Visit 1 ECG.
- Vital signs, physical examination, clinical laboratory tests:
  - The last assessment performed before the first study medication intake of each parameter will be considered in the analysis as the Visit 1 assessment.

### 8.1.8 Exclusion of data from the statistical analysis

Spirometries assessed as being of unacceptable quality will be removed upstream from the clinical database, thus excluded from the statistical analysis.

### 8.1.9 Data listings

All the relevant subject data, including those derived, will be presented in individual subject data listings. All listings will be sorted by treatment regimen, investigational site, patient number, date/time and visit. The patient's sex and age will be stated on each listing. Unless otherwise stated, data listings will be based on all patients randomised.

Unscheduled visit results will be included in date/time chronological order within patient listings, but will not be tabulated.

## 8.2 Subject disposition

All patients who provided informed consent will be included in a summary of patient accountability. The number of subjects screened, the number of screen failures, the frequency of patients randomised (by treatment regimen and overall), the frequency and percentage of patients in the Safety population, in the ITT population, in the PP population and in the PK population (by treatment regimen and overall) will be summarised.

Subject disposition information will be summarised by treatment regimen and overall. The number

of subjects completing and withdrawing study drug intake, completing Acute Exacerbation Phase, completing and withdrawing from the study will be tabulated in the study disposition table which will also include the reasons for treatment discontinuation and early withdrawal of the patient as reported on the eCRF. The summary will also be presented by country.

Finally, the reasons for screen failure as reported on the eCRF will be tabulated.

The follow-up time (number of days from first study treatment to last contact) will be summarised descriptively.

A listing will include the randomisation/kit numbers, randomisation date/time and study disposition data (on all subjects screened).

## 8.3 Protocol deviations

The number of patients excluded from ITT, Safety, PP and PK populations and reasons for exclusion will be summarised by treatment regimen and overall.

Population membership details will be listed, including reason for exclusion from each population (on randomised patients).

All protocol deviations identified will be summarised by treatment regimen and overall.

All protocol deviations identified will be listed based on data recorded on the eCRF and/or protocol deviation Logs (from CTMS).

## 8.4 Demographics and baseline characteristics

Statistical comparisons will be performed whenever possible in order to examine the relationship between each demographics and baseline characteristic and treatment regimen. The associated two-sided p-values representing the comparison across the treatment regimens [one-way ANOVA test, Kruskal-Wallis test (or Wilcoxon Rank-Sum test for pairwise treatment regimens), Pearson's Chi-square test or Fisher's exact test, as appropriate] will be reported in the summary tables and regarded as descriptive.

See Appendix F for SAS code used to implement these standard univariate tests.

For the final analysis, if the Safety and ITT populations are equal, the tables on the ITT population will not be presented if available also on the Safety population.

### 8.4.1 Demographics

Demographic variables will be listed and summarised by treatment regimen and overall. This will include age, sex, race, country of origin, weight, height and BMI. Separate summaries will be produced using the Safety, ITT and PP populations.

### 8.4.2 Smoking status

Smoking status at Screening (ex-smoker or current smoker), duration of smoking (years) and

number of pack-years will be presented by treatment regimen and overall. Separate summaries will be produced using the ITT and PP populations.

### 8.4.3 COPD history

Duration of COPD disease (years), current (last year) severity of the disease, number of moderate or severe COPD exacerbations in the last 12 months before screening [as a continuous and categorical variable (0, 1, 2, 3, >3)], time since last documented COPD exacerbation (months), treatment with systemic corticosteroids or antibiotics (or both) or hospitalisation for the last documented COPD exacerbation, pre-study spirometry results (pre- and post-bronchodilator) from most recent PFT performed outside an exacerbation in the last 12 months will be presented by treatment regimen and overall. Separate summaries will be produced using the ITT and PP populations.

### 8.4.4 Baseline treatment for COPD

COPD treatment category at study entry (Monotherapy: Long-Acting β2-Agonist [LABA] alone, Long-Acting Muscarinic Antagonist [LAMA] alone, Inhaled Corticosteroids [ICS]; Dual therapy: LABA+LAMA, LABA+ICS, LAMA+ICS; Triple therapy: LABA+LAMA+ICS; Other) will be presented by treatment regimen and overall. Separate summaries will be produced using the ITT and PP populations.

### 8.4.5 Current COPD exacerbation data

Duration of current COPD exacerbation symptoms (days) and worsening of respiratory symptoms (breathlessness, wheeze, cough, reduction in exercise tolerance, fever, change in sputum production [change in quantity; aspect purulent vs. non purulent], unusual increase of use of "rescue" medication, other worsened symptoms) will be presented by treatment regimen and overall. Separate summaries will be produced using the ITT and PP populations.

Other exacerbation characteristics data not tabulated above will be listed.

### 8.4.6 Spirometry at Screening and Visit 1 Pre-dose

The following spirometry parameters will be summarised by treatment regimen and overall:

- Screening: FEV1 pre- and post-bronchodilator, FEV1 % of predicted normal value pre- and post-bronchodilator, FVC pre- and post-bronchodilator, FVC % of predicted normal value pre- and post-bronchodilator, FEV1/FVC pre- and post-bronchodilator, FEV1/FVC % of predicted normal value pre- and post-bronchodilator
- Visit 1: FEV1 post-bronchodilator, FEV1 % of predicted normal value post-bronchodilator, FVC post-bronchodilator, FVC % of predicted normal value post-bronchodilator, FEV1/FVC post-bronchodilator, FEV1/FVC % of predicted normal value post-bronchodilator.

Separate summaries will be produced using the Safety, ITT and PP populations.

### 8.4.7 EXACT-PRO at Visit 1 Pre-dose

The EXACT-PRO total score and domain scores at Visit 1 (pre-dose) will be summarised by treatment regimen and overall using the ITT and PP populations.

### 8.4.8 CRQ at Visit 1 Pre-dose

The CRQ total score and domain scores at Visit 1 (pre-dose) will be summarised by treatment regimen and overall using the ITT and PP populations.

### 8.4.9 BODE index at Visit 1 Pre-dose

For the subgroup of patients enrolled in the study under protocols V2.0 and V3.0, the BODE index and subscores at Visit 1 (pre-dose) will be summarised by treatment regimen and overall using the ITT and PP populations.

### 8.4.10 Other Baseline and disease characteristics

Gynaecological history data will be summarised by treatment regimen and overall using the ITT population and listed. Additional investigations performed for COPD exacerbation data (microbiology culture, arterial blood gases, chest X-ray, chest CT scan, other) will be summarised by treatment regimen and overall using the ITT and PP populations and listed. Other Baseline and disease characteristics data will be listed.

### 8.4.11 Medical history and concomitant diseases

A summary of medical history and concomitant diseases will be presented by system organ class (SOC) and preferred term (PT), by treatment regimen and overall using Medical Dictionary for Regulatory Affairs® (MedDRA) Version 20.0 or higher. Separate summaries will be produced using the Safety and ITT populations. A listing of medical history and concomitant diseases will be provided.

Note:

- Medical histories are defined as records in the medical history and concomitant diseases eCRF form which are not ongoing at Screening Visit
- Concomitant diseases are defined as records in the medical history and concomitant diseases eCRF form which are ongoing at Screening Visit.

### 8.4.12 Prior and concomitant medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2017 or later).

Prior and concomitant medications will be summarised by ATC classification and Preferred Name by treatment regimen for the ITT population through frequency distributions and percentages and presented in separate tables for the following groups:

- Previous medication (discontinued prior to study treatment):
  - COPD medications.
- Medication concomitant to study treatment:
  - COPD medications not including medications for COPD exacerbation
  - Medications for COPD exacerbation
  - Non-COPD medications.
- Medications occurring in the Stabilisation Phase (post-treatment medication):
  - Medications for COPD exacerbation.

The following rules to identify COPD medications (administered for COPD exacerbations and for other reasons) are proposed for selecting medications:

**COPD medications:**

Any medications with an indication = 'COPD exacerbation: current/during the study' or 'COPD (non-exacerbation related)' or 'Rescue medication', or which contains 'COPD' or 'CHRONIC OBSTRUCTIVE PULMONARY DISEASE' or 'RESCUE MEDICATION' for 'Indication, specify' field will be considered as COPD medications.

**Medications for COPD exacerbations:**

Any medications with an indication = 'COPD exacerbation: current/during the study' will be considered as medications for COPD exacerbations.

Details for imputing missing or partial start and/or stop dates of medication are described in Section 7.2.2.3.

### 8.4.13 Vital signs at Screening and Visit 1 Pre-dose

Body temperature, systolic (SBP) and diastolic (DBP) blood pressure, pulse rate (PR), respiratory rate (RR), blood oxygen (% HbO2 saturation) assessed pre-salbutamol at Screening and pre-dose at Visit 1 will be summarised by treatment regimen and overall using the Safety population.

### 8.4.14 12-lead ECG at Screening and Visit 1 Pre-dose

The HR, RR, PR, QRS, QT, QTcB and QTcF values obtained from the 12-lead ECG pre-salbutamol at Screening and pre-dose at Visit 1 will be summarised by treatment regimen and overall using the Safety population.

### 8.4.15 Eosinophils at Screening and Visit 1 Pre-dose

Descriptive summaries of eosinophils relative count (%) collected at Screening and pre-dose at Visit 1 will be presented. A summary for eosinophils (%) (<2% or ≥2%) will also be presented. All summaries will be by treatment regimen and overall using the ITT and PP populations.

## 8.5 Extent of exposure

### 8.5.1 Treatment duration

Exposure to randomised IMP (number of days) will be defined as:
(date of last dose of randomised IMP – date of first dose of randomised IMP) + 1

[redacted] and

### 8.5.2 Treatment compliance

IMP administration details, including the number of capsules administered and the complete/partial administration of study drug dose (and reason, if partial) [redacted] by treatment regimen on the ITT population using descriptive statistics.

The total number of doses taken as well as the overall treatment compliance (%) will also be presented by treatment regimen using the ITT population.

The formula for overall compliance (%) calculation is:

Compliance (%) = (total number of capsules administered / 6)*100

## 8.6 Efficacy analyses

This section addresses separately the analyses to be conducted on the primary, secondary and exploratory efficacy variables.

All definitions relative to efficacy and exploratory endpoints are detailed in Section 7.1.4.

### 8.6.1 Analysis methods

Descriptive statistics will be presented for all endpoints. All statistical tests of the efficacy and exploratory endpoints will be two-sided tests and compared to a 5% significance level and all estimates will be presented with two-sided 95% CIs, unless otherwise specified.

Unless otherwise stated, all ANCOVA models and repeated measures models will include the baseline value (last non-missing value collected prior to the first dose of study medication) of the variable as covariate and treatment regimen, severity of airflow limitation at baseline (post-bronchodilator FEV1 at baseline (pre-dose) <30% or ≥30% of predicted normal value), blood eosinophils (%) value at baseline (<2% or ≥2%), time from start of current COPD exacerbation to first IMP dosing (≤2 days, 3-4 days or ≥5 days), presence of cardiovascular comorbidities at screening (yes, no) and COPD exacerbation treatment at screening (systemic corticosteroids only, antibiotics only or both systemic corticosteroids and antibiotics) as fixed effects. Repeated measures models will also include visit/inter-visit period, the treatment by visit/inter-visit period interaction and the baseline by visit/inter-visit period interaction. The adjusted mean difference between treatment regimens will be presented along with a two-sided 95% CI for the time-points of interest.

The calculation of the adjusted means (least squares means) will be based on:

- coefficients for classification effects (i.e., the effects of categorical covariates) proportional to the margins observed in the group of patients analysed;
- effects of quantitative covariates set equal to their mean values in the group of patients analysed.

See Appendix F for details on the calculation of adjusted means (least squares means).

#### 8.6.1.1 Multiplicity

All three treatment regimens will be assessed by pairwise comparisons. No adjustment will be made for multiple comparisons.

#### 8.6.1.2 Treatment by center interaction analysis (multi-center study)

No analysis will be made to assess the treatment-by-center interaction.

### 8.6.2 Analysis of primary efficacy endpoint(s)

The primary efficacy endpoint for this study is the change in FEV1 from baseline (pre-dose) to Day 7, defined as: FEV1 value at Day 7 – FEV1 value at baseline (pre-dose).

#### 8.6.2.1 Primary analysis

The primary analysis of efficacy will be based on the ITT population and observed cases.

The primary analysis will compare each of the treatment regimens together using pairwise comparison tests based on a mixed model for repeated measurements (MMRM) using an unstructured covariance matrix and the Kenward-Roger adjustment for the denominator degrees of freedom. The model will use FEV1 absolute changes at Days 2, 3, 4, 5, 6 and 7, and will include treatment [redacted] severity of airflow limitation at baseline (post-bronchodilator FEV1 at baseline (pre-dose) <30% or ≥30% of predicted normal value), blood eosinophils (%) value at baseline (<2% or ≥2%), time from start of current COPD exacerbation to first IMP dosing (≤2 days, 3-4 days or ≥5 days), presence of cardiovascular comorbidities at screening (yes, no) and COPD exacerbation treatment at screening (systemic corticosteroids only, antibiotics only or both systemic corticosteroids and antibiotics) as fixed effects and baseline FEV1 value as covariate. In addition the baseline FEV1 value-by-visit and the treatment-by-visit interactions will be included in the model.

LSMEAN and standard error (SE) of each treatment regimen as well as the adjusted mean difference between treatment regimens and associated two-sided 95% CIs will be obtained from the MMRM model at Days 2, 3, 4, 5, 6 and 7. Each pairwise treatment regimen comparison will be tested at an alpha level of 5%. Difference will be considered and confirmed between pairwise treatments if the two-sided P-value for the test for difference is below 0.05. P-values of the effects will also be presented.

**Hypotheses:**

The 'superiority' null hypothesis will be:

$H_0$: T2-T1 = 0 (T2 is equivalent to T1) vs the alternative

$H_a$: T2-T1 ≠ 0 (T2 is different to T1)

**MMRM model and SAS code:**

The SAS code used to implement linear mixed model for repeated measures for FEV1 and 95% CIs of differences between treatments will be similar to that shown below:

```
PROC MIXED data = dataset;
    CLASS ID trt visit severity eosino time_symp cv_comorb COPD_trt;
    MODEL change = trt visit trt*visit severity eosino time_symp cv_comorb COPD_trt baseline
    baseline*visit / ddfm=KenwardRoger;
    REPEATED visit / subject=ID type=UN;
    LSMEANS trt*visit /  cl;
    LSMEANS trt / cl;

    LSMESTIMATE trt*visit
        'A vs B: Visit 2'  1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0,
        'A vs B: Visit 3'  0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0,
        'A vs B: Visit 4'  0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0,
        'A vs B: Visit 5'  0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0,
        'A vs B: Visit 6'  0 0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0,
        'A vs B: Visit 7'  0 0 0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0,
        'A vs C: Visit 2'  1 0 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0,
        'A vs C: Visit 3'  0 1 0 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0,
        'A vs C: Visit 4'  0 0 1 0 0 0 0 0 0 0 0 0 0 0 -1 0 0 0,
        'A vs C: Visit 5'  0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 -1 0 0,
        'A vs C: Visit 6'  0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 -1 0,
        'A vs C: Visit 7'  0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 -1,
        'B vs C: Visit 2'  0 0 0 0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0,

        'B vs C: Visit 3'  0 0 0 0 0 0 0 1 0 0 0 0 0 -1 0 0 0 0,
        'B vs C: Visit 4'  0 0 0 0 0 0 0 0 1 0 0 0 0 0 -1 0 0 0,
        'B vs C: Visit 5'  0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 -1 0 0,
        'B vs C: Visit 6'  0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 -1 0,
        'B vs C: Visit 7'  0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 -1 / cl;

    LSMESTIMATE trt;
        'A vs B: Overall' 1 -1 0,
        'A vs C: Overall'1 0 -1,
        'B vs C: Overall'0 1 -1 / cl;
RUN;
```

**Notes**:

- Change represents the change from baseline to each visit of the variable;
- Trt represents the treatment group;
- Visit represents the clinic visit;
- Severity represents the severity of airflow limitation (post-bronchodilator FEV1 at baseline (pre-dose) classified into 2 groups: < 30% or ≥ 30% of predicted normal value);
- Eosino represents the blood eosinophils (%) value at baseline (classified into 2 groups: < 2% or ≥ 2%);
- Time_symp represents the time from start of current COPD exacerbation symptoms to first IMP dosing (≤2 days, 3-4 days or ≥5 days);
- Cv_comorb represents the cardiovascular comorbidities at screening (presence or absence);
- COPD_trt represents the COPD exacerbation treatment at screening (systemic corticosteroids only, antibiotics only or both systemic corticosteroids and antibiotics);
- Baseline represents the baseline value of the variable;
- ID represents the Patient Number;
- Treatment order: 1 = High dose BCT197, 2 = Low dose BCT197; 3 = Placebo
- the 'Overall' least squares means and contrasts will be estimated only for the change from baseline in FEV1.

In case of non-convergence of the above model using an unstructured covariance matrix, the following variance structures will be tested, and based on Akaike's information criteria the best fitting model will be chosen. The variance models that will be considered for the within patient variation in case of non-convergence are in this order: Ante-dependence, Toeplitz, Heterogeneous AR(1), Heterogeneous Compound Symmetry, and Compound Symmetry.

#### 8.6.2.2 Descriptive analysis

FEV1 results (absolute values and changes from baseline) will be summarised by treatment regimen and visit on the ITT population. This descriptive analysis will also be performed based on the PP population.

A figure with adjusted mean change from baseline in FEV1 at each visit by treatment regimen derived from the linear mixed model will be provided on the ITT population. The three treatment regimens will be plotted on the same graph. This graph will also be performed based on the PP population.

Moreover, a bar chart per treatment regimen on the ITT population for the change from baseline in best FEV1 until Day 7 showing the percentage of subjects with changes within the following change from baseline categories: < -200 mL, [-200 mL, -100 mL[, [-100 mL, 0[, …[200 mL, 300 mL[, ≥ 300 mL The increment may be updated if not judged suitable for the range of the data obtained.

#### 8.6.2.3 Sensitivity analyses

**MMRM on PP Population:**

Additionally to assess the robustness of the ITT results, a supportive MMRM analysis using the PP population will be carried out.

**ANCOVA (OC):**

The primary endpoint will be analysed using an ANCOVA model estimating the effect at Day 7, using OC, including treatment, severity of airflow limitation at baseline, blood eosinophils (%) value at baseline, time from start of current COPD exacerbation to first IMP dosing, presence of cardiovascular comorbidities at screening and COPD exacerbation treatment at screening as fixed effects and baseline FEV1 value as a covariate.

The ANCOVA model results will be presented with LSMEAN and standard error (SE) of each treatment regimen as well as the adjusted mean difference between treatment regimens at Day 7 and associated two-sided 95% CIs. Each pairwise treatment regimen comparison will be tested at an alpha level of 5%. Difference will be considered and confirmed between pairwise treatments if the two-sided P-value for the test for difference is below 0.05. P-values of the effects will also be presented.

**ANCOVA Model and SAS code:**

The SAS code used to implement ANCOVA model for FEV1 at Day 7 and 95% CIs of differences between treatments will be similar to that shown below:

```
PROC MIXED data = dataset;
    CLASS trt severity eosino time_symp cv_comorb COPD_trt;
    MODEL change_d7 = trt severity eosino time_symp cv_comorb COPD_trt baseline /
    ddfm=KenwardRoger;
    LSMEANS trt / cl;
    LSMESTIMATE trt;
        'A vs B: Overall' 1 -1 0,
        'A vs C: Overall'1 0 -1,
        'B vs C: Overall'0 1 -1 / cl;
RUN;
```

**Notes**:

- Change_d7 represents the change from baseline to Day 7 of the variable;
- Trt represents the treatment group;
- Severity represents the severity of airflow limitation (post-bronchodilator FEV1 at baseline (pre-dose) classified into 2 groups: < 30% or ≥ 30% of predicted normal value);
- Eosino represents the blood eosinophils (%) value at baseline (classified into 2 groups: < 2% or ≥ 2%);
- Time_symp represents the time from start of current COPD exacerbation symptoms to first IMP dosin[redacted];

- Cv_comorb represents the cardiovascular comorbidities at screening (presence or absence);
- COPD_trt represents the COPD exacerbation treatment at screening (systemic corticosteroids only, antibiotics only or both systemic corticosteroids and antibiotics);
- Baseline represents the baseline value of the variable;
- Treatment order [redacted]
- the 'Overall' least squares means and contrasts will be estimated only for the change from baseline in FEV1.

**MMRM on subgroup of patients enrolled in the study under protocols V4.0 and V5.0:**

For patients enrolled in the study under protocols V4.0 and V5.0, the inclusion criterion 7 regarding post-bronchodilator spirometry was removed, as it was challenging in the acute exacerbation setting to conduct pre- and post- bronchodilator spirometry. Thus, all spirometry measurements were performed 'on bronchodilator' for patients enrolled in the study under protocols V4.0 and V5.0 (i.e. the way of measuring the primary efficacy endpoint has been changed).

Therefore, a MMRM analysis using the ITT population will be performed as a sensitivity analysis on the subgroup of patients enrolled in the study under protocols V4.0 and V5.0.

### 8.6.3 Analysis of secondary efficacy endpoint(s)

The analysis of secondary efficacy endpoints will be performed on the ITT and PP populations.

#### 8.6.3.1 Comparison of FEV1 on Days 3, 10, and 14

A descriptive summary table will be presented for FEV1 absolute values and change for baseline on Days 3, 10, and 14 by treatment regimen and visit.

Change in FEV1 from baseline (pre-dose) to Day 3 will be analysed using an ANCOVA model estimating the effect at Day 3, using OC, including treatment, severity of airflow limitation at baseline, blood eosinophils (%) value at baseline, time from start of current COPD exacerbation to first IMP dosing, presence of cardiovascular comorbidities at screening and COPD exacerbation treatment at screening as fixed effects and baseline FEV1 value as a covariate.

The ANCOVA model results will be presented with LSMEAN and standard error (SE) of each treatment regimen as well as the adjusted mean difference between treatment regimens at Day 3 and associated two-sided 95% CIs. Each pairwise treatment regimen comparison will be tested at an alpha level of 5%. P-values of the effects will also be presented.

A similar ANCOVA model will be used for analysis of:

- Change in FEV1 from baseline to Day 10
- Change in FEV1 from baseline to Day 14.

Additionally, similar analyses as detailed above (descriptive summary table and ANCOVA model) will be performed for:

- Comparison of FVC on Days 3, 7, 10, and 14 (Note: ANCOVA model includes baseline FVC value as a covariate)
- Comparison of FEV1/FVC on Days 3, 7, 10, and 14 (Note: ANCOVA model includes baseline FEV1/FVC value as a covariate).

Furthermore, descriptive summary tables will be presented for the following spirometry parameters (i.e. absolute values and change for baseline on Days 3, 7, 10, and 14 by treatment regimen and visit):

- FEV1 % of predicted normal value
- FVC % of predicted normal value
- FEV1/FVC % of predicted normal value.

#### 8.6.3.2 Normalisation of spirometry parameters over time compared with the most recent test performed within the last 12 months outside an exacerbation

The number and proportion of patients normalised for FEV1 (i.e. FEV1 returns to a value ≥ 89% of the most recent FEV1 value measured within the last 12 months outside an exacerbation) at each visit will be reported by treatment regimen and Pearson's Chi-square test (or Fisher's exact test as appropriate) will be applied to compare normalisation rates at each visit between treatment regimens (two-sided test at 5% alpha level).

Moreover, a bar chart will be presented per treatment regimen for the normalisation of FEV1 at each visit showing the percentage of subjects normalised compared with the most recent test performed within the last 12 months outside an exacerbation.

A similar analysis will be used for:

- Normalisation of FEV1/FVC (i.e. FEV1/FVC returns to a value ≥ 89% of the most recent FEV1/FVC value measured within the last 12 months outside an exacerbation) at each visit.

The timepoints to consider for these analyses are Days 1 to 7, Days 10 and 14, and Weeks 8, 12 and 26.

#### 8.6.3.3 Time to improvement in FEV1 value over time

##### 8.6.3.3.1 Time to improvement of 100 mL in FEV1 over time

Time to improvement of 100 mL in FEV1 from baseline will be analysed using the Kaplan-Meier method. Patients without an improvement of 100 mL in FEV1 from baseline or who are discontinued before reaching it will be considered as "censored" patients.

For the study periods Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Days 8-10, Days 11-14, Weeks 3-8, Weeks 9-12 and Weeks 13-26, the number of patients without an improvement of 100 mL in FEV1 from baseline at the beginning of the period, the cumulative number of patients with

an improvement of 100 mL in FEV1 at the end of the period and the probability of improvement of 100 mL in FEV1 at the end of the period with the associate two-sided 95% CIs will be presented by treatment regimen. The point estimates and the relative two-sided 95% CIs will be presented by treatment regimen for the 75$^{th}$, 50$^{th}$ and 25$^{th}$ percentiles. A Kaplan-Meier plot will also be presented. Comparisons between treatment regimens will be performed by means of the log-rank test. The p-values of the pairwise log-rank test comparisons will be displayed on the figure.

See Appendix F for SAS code used to implement Kaplan-Meier method.

#### 8.6.3.3.2 Time to improvement of 80 mL in FEV1 over time

A similar analysis as in Section 8.6.3.3.1 will be performed for the time to improvement of 80 mL in FEV1 from baseline over time.

### 8.6.3.4 Standardised AUC of FEV1 over time

The standardised AUCs of FEV1 (Day 1 to Day 3, Day 1 to Day 7, Day 1 to Day 10 and Day 1 to Day 14) will be derived and summarised with standard descriptive statistics by treatment regimen.

The standardised AUC from Day 1 to Day 14 will be analysed using an ANCOVA model estimating the effect up to Day 14, using OC, including treatment, severity of airflow limitation at baseline, blood eosinophils (%) value at baseline, time from start of current COPD exacerbation to first IMP dosing, presence of cardiovascular comorbidities at screening and COPD exacerbation treatment at screening as fixed effects and baseline FEV1 value as a covariate.

The ANCOVA model results will be presented with LSMEAN and standard error (SE) of each treatment regimen as well as the adjusted mean difference between treatment regimens at Day 14 and associated two-sided 95% CIs. Each pairwise treatment regimen comparison will be tested at an alpha level of 5%. P-values of the effects will also be presented.

A similar ANCOVA model will be used for analysis of:

- Standardised AUC of FEV1 from Day 1 to Day 7
- Standardised AUC of FEV1 from Day 1 to Day 10.

### 8.6.3.5 Normalisation of RR over time (daily from Days 1 to 7, 10 and 14)

The number and proportion of patients normalised for RR (i.e. RR returns to a plateau level, as defined in Section 7.1.4.6) at each visit during the Acute Exacerbation Phase will be reported by treatment regimen and Pearson's Chi-square test (or Fisher's exact test as appropriate) will be applied to compare normalisation rates at each visit between treatment regimens (two-sided test at 5% alpha level).

The timepoints to consider for these analyses are Days 1 to 7, Day 10 and Day 14.

#### 8.6.3.6 Change in RR on Days 3, 7, 10 and 14

A descriptive summary table will be presented for RR absolute values and change from baseline on Days 3, 7, 10, and 14 by treatment regimen and visit.

A graphical representation of the RR distribution using mean plots (mean and SD) will be provided over time per treatment regimen. The three treatment regimens will be plotted on the same graph.

#### 8.6.3.7 Time to improvement based on EXACT-PRO total score

All EXACT-PRO rolling average results available at Day 3, 5, 7, 10, 14 and 29 will be summarised at each visit by treatment regimen using descriptive statistics. The improvements (changes) in EXACT-PRO rolling average from baseline (Day 1 pre-dose) will also be summarised at Day 3, 5, 7, 10, 14 and 29 by treatment regimen.

MMRM analysis using an unstructured covariance matrix and the Kenward-Roger adjustment for the denominator degrees of freedom will be performed for statistical comparison of treatment regimens with improvement in EXACT-PRO rolling average as an outcome. Model will consider treatment, severity of airflow limitation at baseline, blood eosinophils (%) value at baseline, time from start of current COPD exacerbation to first IMP dosing, presence of cardiovascular comorbidities at screening and COPD exacerbation treatment at screening as fixed effects and baseline EXACT-PRO Rolling Average score as covariate. In addition the baseline score-by-visit and the treatment-by-visit interactions will be included in the model.

LSMEAN and standard error (SE) of each treatment regimen, difference of LSMEANS between treatment regimens and their associated two-sided 95% CIs and corresponding two-sided P-values for Day 3, Day 5, Day 7, Day 10, Day 14 and Day 29 will be estimated by the model. P-values of the effects will also be presented.

The unstructured covariance matrix (which does not presume a particular correlation structure for repeated measurements within patients over time) will be used to adjust for the within-patient error variance covariance. In case model fails to converge, other covariance matrix structures will be considered in the sequence of Ante-dependence, Toeplitz, Heterogeneous AR(1), Heterogeneous Compound Symmetry, and Compound Symmetry.

Similar descriptive analysis and MMRM analysis as above will be performed for each of the 3 EXACT-PRO subscores.

The following figure will be produced for the EXACT-PRO total score and each of the 3 EXACT-PRO subscores:

- Mean EXACT-PRO Rolling Average over time for Day 1 to Day 29 by treatment regimen

Improvement based on EXACT-PRO total score is defined as a decrease in the Rolling Average EXACT score ≥ 9 points from the previous day's Maximum Observed Value during an event.

Time to EXACT-PRO improvement will be analysed using the Kaplan-Meier method. Patients without any EXACT-PRO improvement from baseline over the observed period (Day 1 to Day 29) or who are discontinued before reaching it will be considered as "censored" patients.

For the following study periods: Day 1, Days 2-3, Days 4-5, Days 6-7, Days 8-10, Days 11-14 and Days 15-29, the number of patients without an improvement of EXACT-PRO total score from baseline at the beginning of the period, the cumulative number of patients with an EXACT-PRO improvement at the end of the period and the probability of improvement at the end of the period with the associate two-sided 95% CIs will be presented by treatment regimen. The point estimates and the relative two-sided 95% CIs will be presented by treatment regimen for the 75$^{th}$, 50$^{th}$ and 25$^{th}$ percentiles. A Kaplan-Meier plot will also be presented. Comparisons between treatment regimens will be performed by means of the log-rank test. The p-values of the pairwise log-rank test comparisons will be displayed on the figure.

#### 8.6.3.8 Time to recovery based on EXACT-PRO total score

Recovery based on EXACT-PRO total score is defined as the first day in which a patient experiences a persistent, sustained improvement in their condition over the observed period (Day 1 to Day 29). Improvement (as defined above) must be present for 7 consecutive days. The first day of the 7-day period is designated as the first day of Recovery.

Time to EXACT-PRO recovery will be analysed using the Kaplan-Meier method. Patients without any EXACT-PRO recovery from baseline over the observed period (Day 1 to Day 29) or who are discontinued before reaching it will be considered as "censored" patients.

For the following study periods: Day 1, Days 2-3, Days 4-5, Days 6-7, Days 8-10, Days 11-14 and Days 15-29, the number of patients without a recovery of EXACT-PRO total score from baseline at the beginning of the period, the cumulative number of patients with an EXACT-PRO recovery at the end of the period and the probability of recovery at the end of the period with the associate two-sided 95% CIs will be presented by treatment regimen. The point estimates and the relative two-sided 95% CIs will be presented by treatment regimen for the 75$^{th}$, 50$^{th}$ and 25$^{th}$ percentiles. A Kaplan-Meier plot will also be presented. Comparisons between treatment regimens will be performed by means of the log-rank test. The p-values of the pairwise log-rank test comparisons will be displayed on the figure.

#### 8.6.3.9 Standardised AUC of EXACT-PRO over time

The standardised AUCs of EXACT-PRO (Day 1 to Day 3, Day 1 to Day 5, Day 1 to Day 7, Day 1 to Day 10, Day 1 to Day 14, Day 1 to Day 29) will be derived and summarised with standard descriptive statistics by treatment regimen.

The standardised AUC from Day 1 to Day 14 will be analysed using an ANCOVA model estimating the effect up to Day 14, using OC, including treatment, severity of airflow limitation at baseline, blood eosinophils (%) value at baseline, time from start of current COPD exacerbation to

first IMP dosing, presence of cardiovascular comorbidities at screening and COPD exacerbation treatment at screening as fixed effects and baseline EXACT-PRO Rolling Average score as a covariate.

The ANCOVA model results will be presented with LSMEAN and standard error (SE) of each treatment regimen as well as the adjusted mean difference between treatment regimens at Day 14 and associated two-sided 95% CIs. Each pairwise treatment regimen comparison will be tested at an alpha level of 5%. P-values of the effects will also be presented.

A similar ANCOVA model will be used to analyse the standardised AUC of EXACT-PRO from Day 1 to Day 7 and from Day 1 to Day 10.

All the analyses above will be repeated for each of the 3 EXACT-PRO subscores AUCs.

#### 8.6.3.10 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

All EXACT-PRO rolling average scores available will be summarised at baseline (Day 1 pre-dose) and at specific timepoints during the Acute Exacerbation Phase (Day 3, Day 5, Day 7, Day 10, Day 14) by treatment regimen using descriptive statistics. The improvements (changes) in EXACT-PRO rolling average score from baseline (Day 1 pre-dose) will also be summarised at these timepoints by treatment regimen (See SAP Section 8.6.3.7). Considering Stabilisation Phase, All EXACT-PRO rolling average scores available will be summarised at baseline (Stabilisation Phase), Day 29 (end of Week 4), Day 57 (end of Week 8), Day 85 (end of Week 12), Day 113 (end of Week 16), Day 141 (end of Week 20), Day 169 (end of Week 24) and Week 26 Visit during the Stabilisation Phase by treatment regimen using descriptive statistics. The changes in EXACT-PRO rolling average score from baseline (Stabilisation Phase) will also be summarised at these timepoints by treatment regimen.

The following figures will be produced for the EXACT-PRO rolling average score:

- Mean EXACT-PRO rolling average score over time by treatment regimen (Acute Exacerbation Phase and Stabilisation Phase separately).
- Mean EXACT-PRO rolling average score change from baseline over time by treatment regimen (Acute Exacerbation Phase and Stabilisation Phase separately).

The same analysis as above will be performed for each of the 3 EXACT-PRO subscores.

#### 8.6.3.11 Number of COPD-related exacerbations during the study derived from 'Acute Exacerbation COPD' form of the eCRF

COPD-related exacerbations during the study derived from the 'Acute Exacerbation COPD' form of the eCRF will be considered for this analysis.

Only COPD exacerbations with symptoms start date ≥ first study treatment intake on the form will be included in the analysis. The 'date when symptoms started' recorded on the form will be defined as the start date of the COPD exacerbation.

The number and the percentage of patients with COPD exacerbations, the number of COPD exacerbations and the total follow-up time in years will be summarised by treatment regimen.

The rate of COPD exacerbations per patient per year will be calculated for each treatment regimen using a weighted approach (which consists of pooling all patients of a treatment regimen and dividing the total number of COPD exacerbations by the total follow-up time).

The number and the percentage of patients with COPD exacerbations, the number of COPD exacerbations and the COPD exacerbation rate per patient per year as above will also be presented by treatment regimen for each of the following types of COPD exacerbation:

- Mild COPD exacerbations (intensity recorded as 'Mild' on the form)
- Moderate COPD exacerbations (intensity recorded as 'Moderate' on the form)
- Severe COPD exacerbations (intensity recorded as 'Severe' on the form)
- Moderate/Severe COPD exacerbations (intensity recorded as 'Moderate' or 'Severe' on the form)
- COPD exacerbations resulting in death (i.e. COPD-related deaths; serious criteria 'Results in death' ticked on the form)
- COPD exacerbations requiring hospitalisation (i.e. serious criteria 'Requires in-patient hospitalisation or prolongs existing hospitalisation' ticked on the form).

Additionally (and more generally), the number (%) of patients with COPD exacerbations and the number of COPD exacerbations will be presented by treatment regimen for each of the following category:

- COPD exacerbations treated with systemic corticosteroids only (box ticked on the form)
- COPD exacerbations treated with antibiotics only (box ticked)
- COPD exacerbations treated with systemic corticosteroids and antibiotics (both boxes ticked)
- COPD exacerbations requiring invasive ventilation support (box ticked)
- COPD exacerbations requiring non-invasive ventilation support (box ticked)
- COPD exacerbations requiring Intensive Care Unit (ICU) admission (box ticked)
- COPD exacerbations with each of the following aetiologies: Infection, Environmental pollutants, Extrapulmonary co-morbidities, Concomitant pulmonary co-morbidities, Allergic, Other, Missing (if no aetiology was recorded). A multiple aetiology is possible: in this case the exacerbation will be counted in all the relevant categories.

The proportion of patients with COPD-related exacerbations during the study will be compared between treatment regimens using Pearson's Chi-square test (or Fisher's exact test as appropriate)

(two-sided test at 5% alpha level). This comparison will also be made for mild COPD-related exacerbations, for moderate COPD-related exacerbations, for severe COPD-related exacerbations and for moderate/severe COPD-related exacerbations separately.

Finally, the following acute COPD exacerbation characteristics data (from 'Acute Exacerbation COPD' form of the eCRF) will be summarised by treatment regimen and overall for ITT and PP populations: duration of acute COPD exacerbation symptoms (days), time until complete recovery from the acute COPD exacerbation (days) (if completely recovered), COPD medication category (systemic corticosteroids/antibiotics) for treating the acute exacerbation, hospitalisation data, oxygen therapy and ventilation support data, worsening of respiratory symptoms (breathlessness, wheeze, cough, reduction in exercise tolerance, fever, change in sputum production [change in quantity; aspect purulent vs. non purulent], unusual increase of use of "rescue" medication, other worsened symptoms) and COPD exacerbation aetiology (primary and secondary reasons). Likewise, additional investigations performed for acute COPD exacerbation data (microbiology culture, arterial blood gases, chest X-ray, chest CT scan, other) will be summarised by treatment regimen and overall using the ITT and PP populations. For patients who experienced more than one further COPD exacerbation after the initial COPD exacerbation, the most recent COPD exacerbation will be considered for tabulations.

#### 8.6.3.12 Number of COPD-related deaths during the study

See section 8.6.3.11 for the derivation of COPD-related deaths.

The proportion of patients with a COPD-related death during the study will be compared between treatment regimens using Fisher's exact test (two-sided test at 5% alpha level).

#### 8.6.3.13 Time to next COPD exacerbation

##### 8.6.3.13.1 Time to next COPD exacerbation derived from 'Acute Exacerbation COPD' form of the eCRF

See section 8.6.3.11 for the derivation of COPD-related exacerbations.

Time to next COPD exacerbation will be analysed using the Kaplan-Meier method. Patients without a COPD exacerbation or who are discontinued before having it will be considered as "censored" patients.

For the following study periods: [0-4) weeks, [4-8) weeks, [8-12) weeks, [12-16) weeks, [16-20) weeks and [20-26) weeks, the number of COPD exacerbation-free patients at the beginning of the period, the cumulative number of patients with COPD exacerbation at the end of the period and the probability of having experienced a COPD exacerbation at the end of the period with the associate two-sided 95% CIs will be presented by treatment regimen. The point estimates and the relative two-sided 95% CIs will be presented by treatment regimen for the $75^{th}$, $50^{th}$ and $25^{th}$ percentiles. A Kaplan-Meier plot will also be presented. Comparisons between treatment regimens will be

performed by means of the log-rank test. The p-values of the pairwise log-rank test comparisons will be displayed on the figure.

A similar analysis using the Kaplan-Meier method will be performed for:

- Time to next mild COPD exacerbation (intensity recorded as 'Mild' on the form)
- Time to next moderate COPD exacerbation (intensity recorded as 'Moderate' on the form)
- Time to next severe COPD exacerbation (intensity recorded as 'Severe' on the form)
- Time to next moderate/severe COPD exacerbation (intensity recorded as 'Moderate' or 'Severe' on the form).

#### 8.6.3.13.2 Time to next COPD exacerbation based on EXACT-PRO total score

COPD-related exacerbations during the Stabilisation Phase based on EXACT-PRO total score will be considered for this analysis.

Appendix C describes the EXACT raw scores and EXACT scoring instructions to compute the EXACT daily scores and event frequency, duration and severity.

Time to next COPD exacerbation during the Stabilisation Phase will be analysed using the Kaplan-Meier method. Patients without a COPD exacerbation or who are discontinued before having it will be considered as "censored" patients.

For the following study periods in the Stabilisation phase: [2-6) weeks, [6-10) weeks, [10-14) weeks, [14-18) weeks, [18-22) weeks and [22-26) weeks, the number of COPD exacerbation-free patients at the beginning of the period, the cumulative number of patients with COPD exacerbation at the end of the period and the probability of having experienced a COPD exacerbation at the end of the period with the associate two-sided 95% CIs will be presented by treatment regimen. The point estimates and the relative two-sided 95% CIs will be presented by treatment regimen for the $75^{th}$, $50^{th}$ and $25^{th}$ percentiles. A Kaplan-Meier plot will also be presented. Comparisons between treatment regimens will be performed by means of the log-rank test. The p-values of the pairwise log-rank test comparisons will be displayed on the figure.

### 8.6.3.14 Time from hospitalisation admission until the subject is medically ready for discharge (current COPD)

Time from hospitalisation admission until the subject is medically ready for discharge (current COPD) will be analysed using the Kaplan-Meier method. Only patients with initial hospitalisation for COPD date on or prior to Study Day 1 (i.e. in hospital on Day 1) are included in this analysis. Patients who are discontinued before being medically ready for discharge will be considered as "censored" patients.

For the following study periods: [0-1) days, [1-2) days, [2-3) days, [3-4) days, [4-5) days, [5-6) days, [6-7) days, [7-8) days, [8-9) days, [9-10) days, [10-11) days, [11-12) days, [12-13) days, [13-14) days and [14 days-End of Study], the number of patients not medically ready for discharge at the beginning of the period, the cumulative number of patients medically ready for discharge at the

end of the period and the probability of being medically ready for discharge at the end of the period with the associate two-sided 95% CIs will be presented by treatment regimen. The point estimates and the relative two-sided 95% CIs will be presented by treatment regimen for the 75$^{th}$, 50$^{th}$ and 25$^{th}$ percentiles. A Kaplan-Meier plot will also be presented. Comparisons between treatment regimens will be performed by means of the log-rank test. The p-values of the pairwise log-rank test comparisons will be displayed on the figure.

#### 8.6.3.15 Percentage of days with intake of COPD rescue therapy

Based on 'Rescue Medication' form of the eCRF, a descriptive summary of the number and proportion of subjects requiring COPD rescue therapy will be provided for each visit per treatment regimen. Moreover, the COPD rescue medication category (Monotherapy: Short-Acting β2-Agonist [SABA] alone, Short-Acting Muscarinic Antagonist [SAMA] alone, Long-Acting β2-Agonist [LABA] alone; Dual therapy: SABA+SAMA, SABA+Inhaled Corticosteroids [ICS], LABA+ICS, LABA+SAMA, LABA+SABA; Other) will be presented for each visit per treatment regimen.

Additionally, the percentage of days with intake of COPD rescue therapy (see Section 7.1.4.12 for further details on calculation) will be summarised for each inter-visit period, for the Acute Exacerbation Phase and for the Stabilisation Phase separately, using descriptive statistics by treatment regimen.

### 8.6.4 Analysis of exploratory endpoint(s)

The analysis of exploratory endpoints will be performed on the ITT and PP populations.

#### 8.6.4.1 Exploratory composite scale endpoints at Weeks 8, 12 and 26

The cumulative proportion of patients presenting each of the criteria below during the study will be summarised per treatment regimen at Days 30, 60, 90, 120, 150 and 180 and compared between treatment regimens at each timepoint using Pearson's Chi-square test (or Fisher's exact test as appropriate) (two-sided test at 5% alpha level):

- Worsening of symptoms warranting the addition of another antibiotic or initiation of a new antibiotic
- Worsening of symptoms warranting an increase in dose of oral corticosteroids or initiation of new oral corticosteroids
- Worsening of symptoms requiring additional treatment regimen of oral corticosteroids and/or antibiotics after completion of the initial regimen
- Re-hospitalisation due to worsening of COPD and requiring additional treatment during the duration of the study due to an exacerbation of respiratory symptoms (emergency room admission for longer than 24 hours will qualify as a hospitalisation)
- COPD-related death.

Moreover, the cumulative incidence of CTF (i.e. any one of the individual criteria above is met) will be evaluated at Days 30, 60, 90, 120, 150 and 180 and compared between treatment regimens at each timepoint using Pearson's Chi-square test (or Fisher's exact test as appropriate) (two-sided test at 5% alpha level).

A bar chart will be presented per treatment regimen showing the cumulative incidence of CTF at Days 30, 60, 90, 120, 150 and 180.

In addition, time to CTF will be analysed using the Kaplan-Meier method. Patients who don't meet any one of the individual criteria above or who are discontinued before having it will be considered as "censored" patients.

For the following study periods: [0-4) weeks, [4-8) weeks, [8-12) weeks, [12-16) weeks, [16-20) weeks and [20-26) weeks, the number of clinical treatment failure-free patients at the beginning of the period, the cumulative number of patients with CTF at the end of the period and the probability of having experienced a CTF at the end of the period with the associate two-sided 95% CIs will be presented by treatment regimen. The point estimates and the relative two-sided 95% CIs will be presented by treatment regimen for the $75^{th}$, $50^{th}$ and $25^{th}$ percentiles. A Kaplan-Meier plot will also be presented. Comparisons between treatment regimens will be performed by means of the log-rank test. The p-values of the pairwise log-rank test comparisons will be displayed on the figure.

#### 8.6.4.2 Change in CRQ from Baseline at Day 14 and Weeks 8, 12 and 26

This exploratory endpoint will be analysed separately during the Acute Exacerbation Phase (from Study Day 1 until Day 14 included) and the Stabilisation Phase (from Day 14 until Week 26).

The CRQ total score and domain scores will be summarised at each visit by treatment group using descriptive statistics. Changes in CRQ from baseline (Visit 1 pre-dose) will be summarised at Day 14 during the Acute Exacerbation Phase by treatment regimen. Changes in CRQ from baseline (Visit 9, Day 14) will also be summarised at each post-baseline visit (Weeks 8, 12 and 26) during the Stabilisation Phase by treatment regimen.

Change in CRQ total score from baseline (Visit 1 pre-dose) to Day 14 (Acute Exacerbation Phase) will be analysed using an ANCOVA model estimating the effect at Day 14, using OC, including treatment, severity of airflow limitation at baseline (pre-dose), blood eosinophils (%) value at baseline (pre-dose), time from start of current COPD exacerbation to first IMP dosing, presence of cardiovascular comorbidities at screening and COPD exacerbation treatment at screening as fixed effects and baseline CRQ total score (Visit 1 pre-dose) as a covariate.

The ANCOVA model results will be presented with LSMEAN and standard error (SE) of each treatment regimen as well as the adjusted mean difference between treatment regimens at Day 14 and associated two-sided 95% CIs. Each pairwise treatment regimen comparison will be tested at an alpha level of 5%. P-values of the effects will also be presented.

A similar ANCOVA analysis as above will be performed for each of the 3 CRQ domain scores during the Acute Exacerbation Phase.

MMRM analysis using an unstructured covariance matrix and the Kenward-Roger adjustment for the denominator degrees of freedom will be performed for statistical comparison of treatment regimens during the Stabilisation Phase with change in CRQ total score as an outcome. Model will consider treatment, severity of airflow limitation at baseline (pre-dose), blood eosinophils (%) value at baseline (pre-dose), time from start of current COPD exacerbation to first IMP dosing, presence of cardiovascular comorbidities at screening and COPD exacerbation treatment at screening as fixed effects and baseline CRQ total score (Visit 9/Day 14) as covariate. In addition the baseline CRQ total score-by-visit and the treatment-by-visit interactions will be included in the model.

LSMEAN and standard error (SE) of each treatment regimen, difference of LSMEANS between treatment regimens and their associated two-sided 95% CIs and corresponding two-sided P-values for Weeks 8, 12 and 26 (Stabilisation Phase) will be estimated by the model. P-values of the effects will also be presented.

The unstructured covariance matrix (which does not presume a particular correlation structure for repeated measurements within patients over time) will be used to adjust for the within-patient error variance covariance. In case model fails to converge, other covariance matrix structures will be considered in the sequence of Ante-dependence, Toeplitz, Heterogeneous AR(1), Heterogeneous Compound Symmetry, and Compound Symmetry.

A similar MMRM analysis as above will be performed for each of the 3 CRQ domain scores during the Stabilisation Phase.

A figure with adjusted mean change from baseline (Visit 9/Day 14) in CRQ total score and domain scores at each visit during the Stabilisation Phase by treatment regimen derived from the linear mixed model will also be provided for each score.

#### 8.6.4.3 Cumulative oral/IV steroid dose during the duration of current COPD exacerbation

A descriptive summary table will be presented by treatment regimen for the cumulative oral/IV steroid dose (prednisone equivalent dose) during the duration of current COPD exacerbation. The cumulative prednisone dose will be compared between treatment regimens using a one-way ANOVA test, and the associated two-sided p-value will be reported in the summary table.

Should the normality assumptions for cumulative prednisone dose not be met (the skewness and kurtosis measurements will be considered as supportive indicators), the relationship between cumulative prednisone dose and treatment regimen will be tested using the non-parametric approach of Kruskal-Wallis test (or Wilcoxon Rank-Sum test for pairwise treatment regimens).

#### 8.6.4.4 Change in inflammatory blood biomarkers

Blood biomarkers parameters (IL-6, TNF-α, Fibrinogen, Hs-CRP, MPO) will be measured on days 1 to 7, days 10 and 14, and at Week 8, 12 and 26.

Biomarker data are reported as concentration results, measured using a specific assay with a working range defined by the two limits: Lower limit of quantification (LLOQ) and Upper limit of quantification (ULOQ). Values which fall below the LLOQ or above the ULOQ are reported as < LLOQ * dilution factor (dilution factor: if sample diluted and concentration measured still below LLOQ) and > ULOQ * dilution factor, respectively.

All results for the above biomarker parameters, if collected, will be summarised on the ITT and PP populations by descriptive statistics stratified by treatment regimen and time-point, and including the geometric mean and coefficient of variation. Changes in the biomarker concentrations from baseline (Study Day 1 pre-dose) will be also summarised at each post-baseline time-point.

In the summary table, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included.

In case of censored values (values below the LLOQ and/or values above the ULOQ), the values reported as <LLOQ will be imputed as 0.5*LLOQ and values reported as >ULOQ will be imputed as 1.5*ULOQ.

#### 8.6.4.5 Change from Baseline in mMRC dyspnoea scale over time

This exploratory endpoint will be analysed separately during the Acute Exacerbation Phase (from Study Day 1 until Day 14 included) and the Stabilisation Phase (from Day 14 until Week 26).

The mMRC dyspnoea scale (graded from 0 to 4) will be summarised at each visit by treatment regimen using descriptive statistics. Changes in mMRC dyspnoea scale from baseline (Visit 1 pre-dose) will be summarised at each post-baseline visit (Day 7 and Day 14) during the Acute Exacerbation Phase by treatment regimen. Changes in mMRC dyspnoea scale from baseline (Visit 9, Day 14) will also be summarised at each post-baseline visit (Weeks 8, 12 and 26) during the Stabilisation Phase by treatment regimen.

MMRM analysis using an unstructured covariance matrix and the Kenward-Roger adjustment for the denominator degrees of freedom will be performed for statistical comparison of treatment regimens with change in mMRC as an outcome. MMRM analyses will be done separately for the Acute Exacerbation Phase and for the Stabilisation Phase. Both models will consider treatment, severity of airflow limitation at baseline (pre-dose), blood eosinophils (%) value at baseline (pre-dose), time from start of current COPD exacerbation to first IMP dosing, presence of cardiovascular comorbidities at screening and COPD exacerbation treatment at screening as fixed effects and baseline mMRC (Visit 1 pre-dose for the Acute Exacerbation Phase, Visit 9/Day 14 for the Stabilisation Phase) as covariate. In addition the baseline mMRC-by-visit and the treatment-by-

visit interactions will be included in the model.

LSMEAN and standard error (SE) of each treatment regimen, difference of LSMEANS between treatment regimens and their associated two-sided 95% CIs and corresponding two-sided P-values for Day 7, Day 14 (Acute Exacerbation Phase) and Weeks 8, 12 and 26 (Stabilisation Phase) will be estimated by the model. P-values of the effects will also be presented.

The unstructured covariance matrix (which does not presume a particular correlation structure for repeated measurements within patients over time) will be used to adjust for the within-patient error variance covariance. In case model fails to converge, other covariance matrix structures will be considered in the sequence of Ante-dependence, Toeplitz, Heterogeneous AR(1), Heterogeneous Compound Symmetry, and Compound Symmetry.

A figure with adjusted mean change from baseline (Visit 1 pre-dose) in mMRC dyspnoea scale at each visit during the Acute Exacerbation Phase by treatment regimen derived from the linear mixed model will be provided. A similar figure with adjusted mean change from baseline (Visit 9/Day 14) in mMRC dyspnoea scale will also be provided for the Stabilisation Phase separately.

#### 8.6.4.6 BODE index at Day 14

A descriptive summary table will be presented for BODE index at Day 14 by treatment regimen. BODE index at Day 14 will be compared between treatment regimens using a one-way ANOVA test, and the associated two-sided p-value will be reported in the summary table.

Should the normality assumptions for BODE index at Day 14 not be met (the skewness and kurtosis measurements will be considered as supportive indicators), the relationship between BODE index at Day 14 and treatment regimen will be tested using the non-parametric approach of Kruskal-Wallis test (or Wilcoxon Rank-Sum test for pairwise treatment regimens).

For the subgroup of patients enrolled in the study under protocols V2.0 and V3.0, a separate descriptive summary table will be presented for BODE index at baseline (Visit 1 pre-dose), Day 7, Day 14, Week 8, Week 12 and Week 26 by treatment regimen. Due to the small number of patients involved, no statistical comparison between treatment regimens will be performed.

### 8.7 Safety analyses

All definitions relative to safety endpoints are detailed in Section 7.1.5.

All the safety analyses will be based on the Safety population (treated subject) and will be performed for all safety variables specified below.

In order to assess the safety and tolerability of two different dosing regimens of BCT197 added to SoC versus placebo added to SoC in patients with severe acute exacerbations of COPD, all subjects will have routine safety monitoring throughout the study, including TEAEs/SAEs, TEAEs of special interest (pneumonia, rash/acneiform dermatitis/pruritus, cervical/vaginal inflammation,

headache and liver enzymes), 12-Lead ECGs, vital signs, clinical laboratory assessments (haematology, blood chemistry, urinalysis, pregnancy tests) and quantitative sputum cultures.

The safety parameters collected and changes in these parameters from baseline will be summarised for the treatment regimens separately using standard tabulations and listings. The patients who did not receive the treatment planned by the randomisation will be analysed per the treatment received.

No statistical test will be performed.

### 8.7.1 Adverse events

All AEs will be classified by SOC and PT according to the MedDRA Version 20.0 or higher.

AEs will be classified as pre-treatment AEs or TEAEs. Additionally, TEAES will be classified as occurring during the Acute Exacerbation Phase (from Study Day 1 until Day 14 included) or occurring during the Stabilisation Phase (after Day 14 until Week 26).

Details for imputing missing or partial start dates of adverse events are described in Section 7.2.2.4.

Acute exacerbations of COPD reported in the 'Acute Exacerbation COPD' form of the eCRF will also be included in the analysis of AEs (tables and listings).

**Notes:**

- Two AEs with the same PT and classified in the same category (pre-treatment AE or TEAE) will be considered as two different events when calculating the "number of events" in the tables.
- Where a subject has the same AE, based on preferred terminology, reported multiple times in the same category (pre-treatment AE or TEAE), the subject will only be counted once at the preferred terminology level in AE frequency tables.
- Where a subject has multiple AEs within the same SOC in the same category (pre-treatment AE or TEAE), the subject will only be counted once at the SOC level in AE frequency tables.

Pre-treatment AEs and TEAEs will be presented separately. Pre-treatment AEs will be presented in the listings only.

An overall summary of AEs will be provided. The total number of events and number and proportion of subjects experiencing any AEs, TEAEs, TEAEs of special interest, AEs related to study medication, SAEs, SAEs related to study medication, severe AEs, AEs leading to permanent discontinuation of study treatment and AEs leading to death will be tabulated for each treatment regimen and overall. This overall summary of AEs will also be provided for TEAEs occurred during the Acute Exacerbation Phase and for TEAEs occurred during the Stabilisation Phase separately.

Additionally, TEAEs, TEAEs of special interest, related TEAEs, serious TEAEs, related SAEs, severe TEAEs, AEs leading to permanent discontinuation of study treatment and AEs leading to

death will be summarised by SOC and PT for each treatment regimen and overall (number and percentage of subjects experiencing at least one AE per PT as well as the number of observed events per PT). All TEAEs will also be summarised separately by maximum severity grade for each SOC and PT and by relationship to study medication for each SOC and PT. These summarisations of TEAEs will also be provided for TEAEs occurred during the Acute Exacerbation Phase and for TEAEs occurred during the Stabilisation Phase separately.

A table presenting the number and percentage of subjects with at least one AE and the number of AEs for the most common treatment-emergent AEs (reported in ≥ 1% of patients in any treatment regimen) will be provided. PTs will be used for tabulation, sorted by decreasing overall frequency. This table will also be presented for TEAEs occurred during the Acute Exacerbation Phase and for TEAEs occurred during the Stabilisation Phase separately.

The number and percentage of subjects with any treatment-emergent pneumonias, pneumonias related to study medication, serious pneumonias, serious pneumonias related to study medication, severe pneumonias, pneumonias leading to permanent discontinuation of study treatment, pneumonias leading to death will be presented by treatment regimen and overall. The number of events will also be displayed. This table will also be presented for treatment-emergent pneumonias occurred during the Acute Exacerbation Phase and for treatment-emergent pneumonias occurred during the Stabilisation Phase separately.

Treatment-emergent pneumonias will be analysed in terms of rate per 1'000 patient per year. The follow-up time (in years) will be calculated using the following formula:

(date of last contact - date of first study treatment + 1) / 365.25

The rate of treatment-emergent pneumonia per 1'000 patient per year will be calculated for each treatment using a weighted approach (which consists of pooling all patients of a treatment regimen and dividing the total number of events by the total follow-up time, multiplying the result by 1000).

All AEs will be presented in full in a comprehensive listing including subject number, treatment regimen, severity, seriousness, actions taken, outcome, relationship to treatment, onset/stop and duration. Details of all AEs (pre-treatment AEs, TEAEs during the Acute Exacerbation Phase and TEAEs during the Stabilisation Phase separately), TEAEs of special interest, SAEs, AEs leading to permanent discontinuation of study treatment and AEs leading to death will be listed separately.

### 8.7.2 Clinical laboratory evaluations

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. The following laboratory parameters will be assessed:

- Blood chemistry:
  - Creatinine
  - Blood urea nitrogen [BUN]
  - Fasting serum glucose
  - Aspartate aminotransferase [AST]
  - Alanine aminotransferase [ALT]
  - Gamma-glutamyl transpeptidase
  - Total bilirubin
  - Albumin
  - Chloride
  - Calcium
  - Phosphorous
  - Uric acid
  - Total protein
  - Sodium
  - Potassium.
- Haematology:
  - Red Blood Cell Count [RBC]
  - White Blood Cell Count [WBC]
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Haemoglobin
  - Haematocrit
  - Platelets
  - INR (not required during the Stabilisation Phase)
  - Prothrombin time (not required during the Stabilisation Phase).
- Urinalysis:
  - Specific gravity
  - pH
  - Protein
  - Glucose
  - Blood.

- Pregnancy test:
  - Serum β-HCG
  - Urinary pregnancy test.

For the purposes of summarisation in both the tables and listings, all clinical laboratory data will be reported in Standard International (SI) units.

If a lab value is reported using a nonnumeric qualifier e.g., less than (<) a certain value, or greater than (>) a certain value, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

Descriptive statistics will be presented for quantitative clinical 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 individual data listings along with the Investigator's assessment.

In addition, the number and percentages of subjects with laboratory values for liver function and enzymes of clinical concern[7] as follows will be presented descriptively per treatment regimen during the Acute Exacerbation Phase.

| **Parameter** | **Level for clinical concern** |
|---|---|
| ALT | > 1.5 times the upper limit of the normal range (ULN)<br>> 2xULN<br>> 3xULN<br>> 5xULN<br>> 10xULN |
| AST | > 1.5xULN<br>> 2xULN<br>> 3xULN<br>> 5xULN<br>> 10xULN |
| Bilirubin Total | > 2xULN<br>> 3xULN |
| ALT/AST and Bilirubin Total | ALT/AST> 3xULN and Bilirubin Total> 2xULN |

Haematology, blood chemistry, pregnancy test results and qualitative urinalysis parameters (protein, glucose and blood) will be listed, including data from scheduled and unscheduled timepoints.

### 8.7.3 Vital signs

Vital signs will be performed at each visit in the Acute Exacerbation Phase and in the Stabilisation Phase.

Descriptive statistics (absolute values and changes from baseline) will be presented for each treatment regimen and time-point for vital sign measurements (body temperature, RR, PR, SBP, DBP, blood oxygen [measured using a pulse oximeter]).

A data listing of vital signs will also be provided.

### 8.7.4 Physical examinations

Physical examination will be performed at each visit in the Acute Exacerbation Phase and in the Stabilisation Phase.

The number and percentage of patients experiencing an abnormal physical examination finding will be presented per body system for each treatment regimen and time-point.

All physical examination data and abnormalities will be listed by subject and body system.

### 8.7.5 Electrocardiograms

A central ECG laboratory will be used. ECG assessments will be performed at each visit in the Acute Exacerbation Phase (Days 1, 3, and 5 pre-dose). For patients enrolled in the study under protocols V4.0 and V5.0, additional ECGs will be performed at any 2 of the 3 IMP dosings (Days 1, 3, or 5) and at PK sample times (pre-dose, 0-2 h post-dose, 4-8 h post-dose, > 12h post-dose).

Descriptive statistics (absolute values and changes from baseline) will be presented for the 12-lead ECG measurements for each treatment regimen and time-point (per visit, and separately for multiple assessments within a visit) for ECG parameters (HR, RR interval, PR interval, QRS interval, QT interval, QTcB interval and QTcF interval). Within a visit change from pre-dose summaries to each post-dose (0-2 h, 4-8 h, > 12h) PK ECG assessment will also be produced. In addition, the overall ECG interpretation will be summarised by presenting the number and percentage of subjects with "Normal", "Abnormal, NCS" and "Abnormal, CS" for each treatment regimen and time-point (per visit, and separately for multiple assessments within a visit).

A separate descriptive summary of ECG assessments will be performed for the subgroup of patients enrolled in the study under protocols V4.0 and V5.0.

A data listing of ECG measurements will be provided.

### 8.7.6 Sputum for microbiology culture

If sputum for microbiology culture is collected for clinical purposes, the results from sputum culture (qualitative and quantitative) will be listed.

### 8.7.7 Other safety assessments

Gynaecological assessment (including assessment of inflammation of cervix and vagina), acute COPD exacerbation assessment, additional investigations for COPD exacerbation, additional investigations for pneumonia and dermatologic assessment data will be listed.

## 8.8 Other analysis

### 8.8.1 Efficacy analyses based on acute exacerbations of COPD adjudication

An independent, external IAC has been set-up to carry out responsibilities as detailed in the Independent Adjudication Committee Charter, Final Version 1.0, dated 07 February 2017.

Specific details regarding procedures for clinical adjudication of the components of the endpoint as well as the adjudication data collection/transfer process are fully described in the following documents:

- IAC Charter
- Systems Requirements Specifications, Final Version 2.0, dated 28 February 2017
- Data Delivery Specification, Final Version 1.0, dated 10 May 2017.

Once subjects have completed study treatment, the events to be adjudicated by the IAC are all new reports of acute exacerbation of COPD and events of hospitalisation due to new exacerbations of COPD (dataset AECOPD – AECOPD Adjudication Assessment). Each Adjudication case will be reviewed independently by each of the three adjudicators. If the adjudicators agree on all non-text fields the case will be complete and final. If they do not agree, they will meet and complete in Consensus.

The data derivations and statistical analyses to be performed based on acute exacerbations of COPD adjudication are described below:

- Number and percentage of patients with positively adjudicated moderate/severe COPD exacerbations will be provided by treatment regimen
- Number of positively adjudicated moderate/severe COPD exacerbations during the study will be provided by treatment regimen
- Rate of positively adjudicated moderate/severe COPD exacerbations per patient per year will be provided for each treatment regimen (same approach as for the non-adjudicated data)
- The proportion of patients with positively adjudicated moderate/severe COPD exacerbations during the study will be compared between treatment regimens using Pearson's Chi-square test (or Fisher's exact test as appropriate) (two-sided test at 5% alpha level)
- The time to next positively adjudicated moderate/severe COPD exacerbation will be analysed using the Kaplan-Meier method. Patients without a positively adjudicated moderate/severe COPD exacerbation or who are discontinued before having it will be

considered as "censored" patients. The same approach as for the non-adjudicated data will be used.

- Similar analyses as above will be performed for positively adjudicated moderate COPD exacerbations and for positively adjudicated severe COPD exacerbations separately.

### 8.8.2 PK/PD analyses

Subjects [redacted] sample to be take
taken 4-8 hours post-dose, and one sample no earlier than 12 hours post-dose.

This plan does not address the PK/PD analyses of BCT197 (nonlinear mixed effects PK/PD modelling evaluating the relationship between BCT197 exposure and efficacy/safety endpoints) for this study. These analyses will be performed by ICON Pharmacokinetics, Pharmacodynamics, Modelling and Simulation Department and will be detailed in a separate analysis plan. Results from the PK/PD modelling will be reported separately from the CSR. An overview of the PK/PD analyses of BCT197 is provided here: "A population PK model for BCT197 will be developed using nonlinear mixed effects and the sparsely sampled PK concentration, from which measures of BCT197 exposure will be derived. If necessary, additional PK data from more intensively sampled studies will be included to support the development of the structural model. The population PK model will also evaluate the potential influence of demographic factors and covariates on the PK of BCT197. A graphical exploration will be undertaken to identify potential relationships between BCT197 exposure and selected efficacy/safety endpoints to be formally evaluated using nonlinear mixed effects modelling (including BCT197 exposure/QTc modelling)".

BCT197 concentrations will be summarised on the PK population by descriptive statistics stratified by BCT197 dose-level and time-point, and including the geometric mean and coefficient of variation.

A graphical representation of the BCT197 concentrations distribution using mean plots (mean and SD) will be provided over time per BCT197 dose-level on the PK population. Both dose-levels will be plotted on the same graph.

### 8.8.3 Subgroup analysis

To verify the internal consistency of the trial data and results, statistical analyses of the primary efficacy endpoint, i.e. summarisation of FEV1 results (absolute values and changes from baseline) by treatment regimen and visit (until Day 7) on the ITT population, will be repeated for the following subgroups of patients:

- Severity of COPD disease at screening (Gold C, Gold D)
- Sex (Males, Females)
- Geographic region (Europe, Rest of World)
- Blood eosinophils relative count (%) at baseline ($< 2\%$, $\geq 2\%$)

- FEV1 % of predicted normal value post-bronchodilator at baseline (based on tertiles)
- FEV1 absolute value post-bronchodilator at baseline (based on tertiles)
- FEV1/FVC % of predicted normal value post-bronchodilator at baseline (based on tertiles)
- FEV1/FVC absolute value post-bronchodilator at baseline (based on tertiles)
- COPD exacerbation aetiology (primary reason) at screening (Infection, Environmental Pollutants, Extrapulmonary Co-morbidities, Concomitant Pulmonary Co-morbidities, Allergic, Other)
- Change in sputum production at screening (No Change, Yes: Purulent; Yes: Non Purulent)
- Cardiovascular comorbidities at screening (Presence, Absence)
- Time from start of current COPD exacerbation to first IMP dosing (≤2 days, 3-4 days or ≥5 days)
- Protocol Version under which the patient was enrolled to (Protocols V2.0 and V3.0, Protocols V4.0 and V5.0).

For each subgroup of patients, the mean change in FEV1 from baseline (pre-dose) to Day 7 will be compared between treatment regimens using a one-way ANOVA test, and the associated two-sided p-value will be reported in the summary table and regarded as descriptive.

Should the normality assumptions for change in FEV1 from baseline (pre-dose) to Day 7 not be met (the skewness and kurtosis measurements will be considered as supportive indicators), the relationship between change in FEV1 from baseline (pre-dose) to Day 7 and treatment regimen will be tested using the non-parametric approach of Kruskal-Wallis test (or Wilcoxon Rank-Sum test for pairwise treatment regimens).

## 8.9 Interim analysis

No formal interim analysis is planned for this study.

However, an independent, external DMC has been set-up to carry out responsibilities as detailed in the Data Monitoring Committee Charter, Final Version 1.0, dated 01 February 2016.

Accumulating unblinded safety data of BCT197 were reviewed periodically (approximately quarterly) by the DMC. Should safety concerns be identified, a decision might be taken to halt the trial.

A separate DMC SAP, Final Version 2.0, dated 13 December 2016, has been developed to describe the data derivations and data summaries to be presented for the DMC analysis of Clinical Protocol MBCT206, for comparing the safety of two different dosing regimens of BCT197 when added to SoC versus placebo added to SoC for the treatment of acute respiratory exacerbations of COPD requiring hospitalisation in adults.

# 9 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

- Definition of PP population:
  The PP definition stated in the protocol was clarified, in that only key inclusion/exclusion criteria with respect to factors likely to affect the assessment of efficacy need to be satisfied to include a subject in the PP population.

- PP analyses:
  A PP analysis was added for the secondary and exploratory efficacy endpoints for this PoC and hypothesis-generating study. This PP analysis was initially planned in the study protocol on the primary efficacy endpoint only.

- Cumulative oral/IV steroid dose analysis:
  The exploratory endpoint specified in the study protocol is "Cumulative oral/IV steroid dose from Day 1 to Day 14 and from Day 14 to Week 26". This analysis was finally performed during the duration of current COPD exacerbation (i.e. from the date when symptoms started until the date when symptoms stopped) upon Mereo's request. Sponsor was more interested in the amount of systemic steroids needed to control the current COPD exacerbation.

## 10 REFERENCES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5. Siddiqui O, et al. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat. 2009;19(2):227-46.
6. EXACT-PRO User Manual Version 8.0 dated March 2016
7. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, FDA. Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Final, July 2009.

# 11 APPENDICES

## Appendix A – Summary of Protocol Amendments - Key Changes

| Amendment | Change | Rationale |
|---|---|---|
| Protocol Version 2.0, Amendment 1 (revisions to Protocol Version 1.0) | Added pulse oximeter measurements as part of vital sign measurements to be carried out | At the request of the FDA |
| Protocol Version 3.0, Amendment 2 (revisions to Protocol Version 2.0) | Laboratory test change: requirement for INR and prothrombin time sampling and testing after Day 14 removed | As the last dose is taken on Day 5, analysis of INR and prothrombin time is only deemed necessary during the Acute Exacerbation Phase |
| Protocol Version 3.0, Amendment 2 (revisions to Protocol Version 2.0) | Reduction of ECG testing from triplicate to a single test | ECG are no longer required in triplicate by the Central Reader |
| Protocol Version 3.0, Amendment 2 (revisions to Protocol Version 2.0) | Addition of inflammation of cervix and vagina as an adverse event of special interest | Align with Investigator's Brochure at the request of the UK Regulatory Agency |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Modification of inclusion criterion 4 to reflect that spirometry in the past 12 months is required but the result does not need to be available before dosing. | Spirometry is being done at screening and this will be used to determine eligibility for the study. Historical data is required for data analysis demography only. If historical values are not available, pre and post bronchodilator spirometry will be conducted during the stabilization phase, for demographic purposes. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Modification of inclusion criterion 5 to allow subjects who have given up smoking in the last 6 months into the study. | The impact of smoking cessation within 6 months is not significant to the patient assessment, within the trial. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Increase of FEV1 to <65 % of the predicted normal value for inclusion criterion 6. | This will facilitate recruitment of the appropriate population and is not anticipated to adversely impact safety of subjects or efficacy outcomes. |

| | | |
|---|---|---|
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Removal of inclusion criterion 7 regarding post-bronchodilator spirometry. | In the acute exacerbation setting it is challenging to conduct pre and post bronchodilator spirometry. Therefore, all spirometry measurements will be performed 'on bronchodilator'. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Update of regular medication requirements for inclusion criterion 9. | Restriction changed to allow the use of any short acting rescue medication to match with standard clinical practice. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Removed exclusion criterion of history of allergic rhinitis and atopic disease. | Exclusion only for allergic asthma needed to ensure COPD is expected diagnosis. Rhinitis and atopic disease exclusion not required. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Removal of macrolide and calcium channels blockers from exclusion criterion 3. | Removed to avoid replication as they are covered by exclusion criterion 9. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Update of exclusion criterion 10 to reflect that only live vaccines should be withheld for 30 days before screening. | Non-live vaccines are required to be withheld for only 14 days, the period of the immune response to the vaccines. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Removal of criterion 14 excluding those in whom anti-muscarinic agents are contraindicated. | Antimuscarinic use is not a requirement for study participation so this exclusion criterion is not required. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Removal of exclusion criterion 20 for concomitant use of agents that prolong the QTc interval. | Recent PK/PD modelling of available clinical data indicates there is no concentration – QTc relationship with BCT197. The recent data, in addition to the available preclinical data, indicate that BCT197 at the concentrations predicted to be achieved would not prolong the QTc interval. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Addition of excluded concomitant medication of P-gp inhibitors to exclusion criterion 19. | P-gp inhibitors were previously included in the list of excluded medications but not included as an exclusion criterion. |

| | | |
|---|---|---|
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Addition of exclusion criteria for subjects with pneumonia, pneumothorax or pulmonary embolus. | Subjects with these conditions should not be enrolled in the study, for subject safety. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Modification of spirometry assessment and timings to reflect that all spirometry will be taken at least 1 hour after regular long acting bronchodilator administration and 30 minutes after a short acting bronchodilator rescue medication has been taken. For patients with acute exacerbation it is not practical to have FEV1 after bronchodilator wash out. | It is necessary to standardize baseline and post study drug assessment of spirometry as much as practically possible. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Modification to timing of ECG assessments. | BCT197 would not be expected to be present in the body at 8, 12 and 26 weeks post dose and so ECGs at these time points have been removed. Additional ECGs have been added at dosing and PK sample times to increase safety monitoring and to allow for PK/PD analysis of QTc data around the time of maximum concentration BCT197 are included. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Collection of baseline information on presence of specific symptoms of acute exacerbation (increased sputum production, increased cough and/or increased dyspnea). | Data required to better characterize the patient population. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Addition of theophylline to permitted concomitant medications. | May form part of standard care. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Six minute walk test has been reduced to single measurement at end of acute exacerbation. | The expectation is that subjects will be unable to perform this test due to their clinical condition in the early part of the exacerbation. A single measurement at |

| | | |
|---|---|---|
| | | day 14 gives adequate data. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | The composite score has been removed from Baseline Visit. | The composite score detects treatment failure so should not be included at Baseline. |
| Protocol Version 4.0, Amendment 3 (revisions to Protocol Version 3.0) | Inclusion of vaginal inflammation evaluation (history and if indicated by symptoms, examination). | Included following regulatory agency feedback. |
| Protocol Version 5.0, Amendment 4 (revisions to Protocol Version 4.0) | Azithromycin is no longer a prohibited medicine as an exclusion criteria | Results of a drug interaction study with BCT197 and azithromycin showed no clinically meaningful impact of concomitant dosing on BCT197 levels |
| Protocol Version 5.0, Amendment 4 (revisions to Protocol Version 4.0) | Clarification in prohibited meds that the P-gp inhibitor Azithromycin is not prohibited | Results of a drug interaction study with BCT197 and azithromycin showed no clinically meaningful impact of concomitant dosing on BCT197 levels |
| Protocol Version 5.0, Amendment 4 (revisions to Protocol Version 4.0) | Removal of exclusion of killed vaccine in last 14 days as exclusion criterion | No safety risk in administering killed vaccine. |
| Protocol Version 5.0, Amendment 4 (revisions to Protocol Version 4.0) | Removal of killed vaccine as a prohibited medication | No safety risk in administering killed vaccine. |
| Protocol Version 5.0, Amendment 4 (revisions to Protocol Version 4.0) | Removal of oral requirement for body temperature | There is no requirement for oral body temperature and any body site (oral, rectal, axillar, etc.) is suitable. |
| Protocol Version 5.0, Amendment 4 (revisions to Protocol Version 4.0) | Removal of exclusion criteria 7 - Subjects requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxemia | Reduction of respiratory testing procedures in the previous protocol amendment (v4) enables patients on long term oxygen therapy to undertake the required assessments during the study. Therefore, there is no longer any need to exclude patients on long term oxygen therapy. |

## Appendix B – Protocol Deviations Criteria List

The list of protocol deviations to be identified and to be included in the body of the CSR is defined as:

- Failure to obtain written informed consent prior to a patient's participation in the study (Randomised/ITT/PP/Safety/PK)
- Patient does not meet one or more of the inclusion criteria (PP)
- Patient meets one or more of the exclusion criteria (PP)
- Disallowed medications, as per Section 10.6 - Concomitant Therapy of the protocol (PP)
- Patient/Investigator unblinded to treatment
- Serious Breach of GCP
- Incorrect treatment allocation/taken wrong study medication (PP)
- Same medication number given to more than one patient
- Non-compliance with IMP administration [redacted] (ITT/PP/Safety/PK)
- Failure to complete spirometry assessments at visits 1-12; in particular failure to complete adequate measurement of the primary variable (i.e. Baseline and/or Day 7 FEV1 values not provided) (ITT/PP)
- Failure to complete BODE at Visit 9
- Failure to complete mMRC at visits 1, 7, 9, 10, 11 and 12
- Failure to obtain PK samples on 2 of the 3 dosing days (PK)
- Failure to complete CRQ at visits 1, 9, 10, 11 and 12
- Failure to report a SAE within timelines required by GCP, the protocol and applicable regulations
- Failure to report AEs of special interest as required by protocol
- Temperature excursion where IMP is stored (IMP dispensed to patient) (PP)
- Expired IMP administered to a patient (PP)
- Drug accountability incomplete to the extent that an IMP kit cannot be 100% traced from sponsor/warehouse to site and back (PP)
- Patient non-compliance with e-diary
- Lack of source data in the patient source – direct entry into the eCRF
- IRB/EC was not constituted in accordance with the establishment requirements
- IRB/EC review was conducted in an inappropriate procedure such as circulation etc. other than normal Meeting
- Study visit out-of-window as defined in the current protocol (PP)
- Missed study visit (PP)
- Missing Central Laboratory assessments
- Missing Respiratory Rate results
- Missing QTc Interval results.

## Appendix C – EXACT Scoring Instructions

### 1. Computing EXACT Daily Scores

**Raw Scores**

Raw scores are assigned to each item response option, as shown in Table 1 of this Appendix. Note that items 3, 8, 9, 10, 11, and 14 have unique scoring instructions. Item responses should be converted to item-level scores as the first step in scoring.

The recommended programming for the electronic EXACT diary does not allow a study patient to skip individual items. If a patient tries to skip a question, a message should appear to prompt the patient to complete the question. Thus, no missing data are expected for individual items in the electronic data capture setting. If missing values do occur for individual items, the scores for that day cannot be calculated and should be set to missing.

**EXACT Total Score**

An EXACT Total score should be computed for each day of diary collection. The EXACT Total score is based on a logit scoring system with conversion to a 0 to 100 scale for ease of interpretation and use. The scores are computed using a simple conversion table, by hand or electronically (e.g., software data interface for ePRO devices or statistical software, such as SAS®). To compute the EXACT Total score:

Convert each original item response code to an item-level raw score, by matching the responses to Table 1 below. For example, for question 1, if the data-collection form or system encodes the response of "Not at all" as code 1, recode it to a zero (0) to match Table 1, question 1. Note that some questions group certain original item response codes into a single item-level raw score; for example, question 3 groups original responses of "A little" and "Some" into the item-level raw score of 1.

Sum the item-level raw scores of the 14 EXACT items to form the raw summed score.

Note: do not sum the original item responses; sum the recoded values obtained in the step described above.

For each raw summed score, look up the corresponding EXACT Total score from Table 2 of this appendix. The EXACT Total score ranges from 0 to 100. Sample SAS program code for converting raw summed scores to the EXACT Total score is provided in Table 4 of this appendix.

If the EXACT Total score is 0, change it to missing. This scoring rule is based on previous validation work demonstrating that moderate-to-severe COPD patients will experience symptom(s) each day, and a score of zero on all 14 EXACT items is likely to represent a situation where in order to complete the diary quickly, the respondent did not accurately report their daily symptom(s).

Where no diary entry exists for a given day, create a record in the data file for that day and enter a missing value for the EXACT Total score. Each day a patient is followed in the study must have a record for the day, even if there is no data and the EXACT Total score is missing.

**Domain Scores**

Three respiratory symptom domains are also embedded within the EXACT measure: Breathlessness, Cough & Sputum, and Chest Symptoms.

To compute domain scores:

Item assignments to domains are as follows. Please note that items 4, 12, 13, and 14 do not correspond to a domain score and are not used in domain-specific analyses.

- Breathlessness – Items 7, 8, 9, 10, and 11
- Cough & Sputum – Items 2 and 3
- Chest Symptoms – Items 1, 5, and 6.

For each day, sum the item-level raw scores of the items comprising the domain to form the domain raw summed score. If no diary entry exists for a given day, leave the domain raw summed score missing.

Each domain raw summed score has its corresponding "EXACT Domain" score. For each domain raw summed score, look up the corresponding EXACT domain score from Table 3 below. If no diary entry exists for a given day, leave the EXACT domain score missing.

If the daily EXACT domain score is 0, change it to missing. This scoring rule is based on previous validation work demonstrating that moderate to severe COPD patients will experience symptom(s) each day, and a score of zero on all 14 EXACT items is likely to represent a situation where in order to complete the diary quickly, the respondent did not accurately report their daily symptom(s).

**2. Computing Event Frequency, Duration, and Severity**

All exacerbation parameters are based on the EXACT Total score.

**Baseline EXACT Total Score**

For studies enrolling patients during a stable baseline period, baseline EXACT values are computed and used to identify the onset of EXACT events.

For MBCT206 study, as there is no stable period during which EXACT-PRO scores are collected prior to administrating the study drug, the definition of the Baseline EXACT-PRO from the user manual will not be used for Acute Exacerbation Phase.

The score and subscores obtained on Day 1 of the EXACT-PRO observation period, which corresponds to Study Day 1, will be used as the baseline for Acute Exacerbation Phase.

Nevertheless, the definition of the Baseline EXACT-PRO from the user manual will be used for Stabilisation Phase. Baseline is defined as a period during which the patient is considered within

his/her condition as stable or their usual state. The Baseline EXACT-PRO score (or subscores) for Stabilisation Phase will therefore be defined as the mean of EXACT-PRO scores from the first 7 days of the Stabilisation Phase (Week 3; Days 15-21), with a minimum of 4 days of available data required to compute the baseline value. If 4 or more of the first 7 days of data are not available, the baseline EXACT-PRO score for Stabilisation Phase will not be calculated.

***Resetting Baseline EXACT Total Score (Stabilisation Phase)***

Over the course of the trial, Baseline should be reset every 4 weeks (28 days) in the absence of an EXACT-based event to allow for improvements or deterioration in disease state over time, as follows:

**Event-free Periods (Stable Reset Baseline – $\text{Baseline}_{SR\#}$)**

For patients who do not experience an EXACT-based event during Weeks 4 to 7 of the study, Baseline is reset beginning Day 1, Week 8. Data from the last 7 days of the 4 week period (Week 7; Days 43–49) are used for this purpose, with a minimum of 4 days of data required to compute the reset value ($\text{Baseline}_{SR1}$; mean within patient-score over 7 days). If fewer than 4 days of data are available, the Baseline will not be reset; the previous Baseline value (i.e. mean of EXACT-PRO scores from the first 7 days of the Stabilisation Phase (Week 3; Days 15-21)) will be used until the next reset period.

Using this reset Baseline ($\text{Baseline}_{SR1}$), the data are examined moving forward from Week 8, Day 1 for evidence of an EXACT-based event during the subsequent 4 weeks (Week 8, Day 1 to Week 11, Day 7). In the absence of such an event, the Baseline is reset again ($\text{Baseline}_{SR2}$) beginning Day 1, Week 12. Data from the last 7 days of the 4 week period (Week 11; Days 1–7) are used for this purpose, with a minimum of 4 days of data required to compute the reset value ($\text{Baseline}_{SR2}$). If fewer than 4 days of data are available, the Baseline will not be reset; the previous Baseline value will be used until the next reset period.

The resetting process continues every 28 days throughout the duration of the study or until an EXACT event occurs (see instructions below).

**Re-Setting Following an EXACT Event (Event Reset Baseline – $\text{Baseline}_{ER\#}$)**

If or when an EXACT event occurs during the Stabilisation Phase, the patient's Baseline value is re-established following recovery. To reset Baseline values following an exacerbation, the patient's mean EXACT score during the fourth week following Recovery (Days 22–28 post-Recovery) is used. If the patient experiences a new EXACT event during this 4 week period (Days 1 to 28 post-Recovery), the Baseline is not reset until the fourth week following Recovery from that subsequent event. A minimum of 4 days of data are required to reset Baseline. If fewer than 4 days of data are available, the Baseline will not be reset; the previous Baseline value (i.e. mean of EXACT-PRO scores from the first 7 days of the Stabilisation Phase (Week 3; Days 15-21)) will be used until the next reset period.

The reset Baseline following Recovery from the first exacerbation ($Baseline_{ER1}$) is used to identify subsequent events during the next 4 week period. In the absence of an event during this 4 week period, the Baseline value is reset again ($Baseline_{ER2}$), beginning Recovery Week 9, Day 1, using data from the final 7 days of the 4-week event-free period (Recovery Week 8; Days 1–7 post-Recovery). If fewer than 4 days of data are available, the Baseline will not be reset; the previous Baseline value will be used until the next reset period.

This process of resetting Baseline in the absence of an EXACT event continues through the duration of the study.

**Event Frequency (Stabilisation Phase)**

Two parameters are required to identify event frequency: (1) Baseline and (2) Onset. Baseline has been previously described for Acute Exacerbation Phase and for Stabilisation Phase. Due to the design of the study, the EXACT-PRO user manual definition of "Onset" will not be used for Acute Exacerbation Phase, and the EXACT-PRO value on Study Day 1 will replace the "Onset" in the definitions. Therefore, event frequency will not be identified for Acute exacerbation Phase.

Nevertheless, the EXACT-PRO user manual definition of "Onset" will be used for Stabilisation Phase. Onset is defined as the first day in which the patient experiences an acute, sustained worsening of their baseline condition. Therefore, event frequency will be identified for Stabilisation Phase.

***Onset***

Onset is identified in 1 of 2 ways: *Either* (1) an increase in EXACT score ≥12 points above the patient's mean Baseline for 2 consecutive days, with Day 1 of the 2 days serving as $Day_1$ (Onset) of the event **OR** (2) an increase ≥9 points above the patient's mean Baseline for 3 consecutive days, with Day 1 of the 3 days serving as $Day_1$ (Onset) of the event. The presence of either constitutes Onset of an event during the Stabilisation Phase. Note that the requirement of consecutive days is the reason the data file must have a record for every day for a patient, even if the EXACT score is missing.

**Event Duration (Stabilisation Phase)**

Event Duration requires identification of the following parameters: (1) Onset; (2) 3-day Rolling Average; (3) Maximum Observed Value; (4) Threshold for Improvement; and (5) Recovery. It is possible that Improvement may occur at multiple timepoints during an event and that this Improvement may or may not reflect full Recovery. As the EXACT-PRO user manual definition of "Onset" will not be used for Acute Exacerbation Phase, event duration will not be identified for Acute Exacerbation Phase. Nevertheless, the 4 other parameters will be identified for Acute Exacerbation Phase as below.

On the other hand, the EXACT-PRO user manual definition of "Onset" will be used and event duration will be identified for Stabilisation Phase. Therefore, the 5 parameters will be identified for

Stabilisation Phase as below.

***Three-day Rolling Average***

A 3-day Rolling Average is used to account for day-to-day variability in EXACT scores. This is operationalized as a 3-day Rolling of the mean EXACT score [$Day_{x-1}$, $Day_x$, $Day_{x+1}$] initiated on Study Day 1 (Onset) and ends on Day 1 of recovery.

The 3-day Rolling Average will be calculated from Study Day 1 to Day 1 of recovery:

- At Day 1, the Rolling Average will be the total score of Study Day 1 (Onset), and will be missing if the total score of Study Day 1 is missing
- At Day 2 the Rolling Average will be the total score of Study Day 2, and will be missing if the total score of Study Day 2 is missing
- The Rolling Average at any other Day x (including Day 1 of recovery) will be computed as the mean of Study $Day_{x-1}$, $Day_x$, $Day_{x+1}$, if at least one of $Day_{x-1}$, $Day_x$, $Day_{x+1}$ is available.

Only 1 of the 3 data points needs to be present for this computation.

Improvement from Day 1 in EXACT-PRO Rolling Average will be calculated as:

Improvement from Day 1 = Rolling Average at Day 1 - Rolling Average at Day x

The improvement from Day 1 in EXACT-PRO Rolling Average will be left missing if the Rolling Average at Day 1 cannot be computed or if it is missing at Day x.

***Maximum Observed Value between Day 1 and Day 14***

The Maximum Observed Value (MOV) is the highest Rolling Average EXACT score observed in the context of an EXACT exacerbation within the first 14 days of the exacerbation (i.e. between Day 1 and Day 14). The MOV is allowed to increase over the first 14 days of an exacerbation. Starting on Day 15 of an exacerbation, the MOV stays at the level on the $14^{th}$ day for the remainder of the exacerbation.

***Threshold for Improvement***

Improvement is defined as a decrease in the Rolling Average EXACT score $\geq 9$ points from the previous day's MOV during an event.

***Recovery***

Recovery is defined as the first day in which a patient experiences a persistent, sustained improvement in their condition over the observed period. Improvement must be present for 7 consecutive days. The first day of the 7-day period is designated as the first day of Recovery ($Day_R$).

Based on the scoring algorithm for Recovery, EXACT exacerbations can be categorized as Recovered, Censored, or Persistent Worsening. Recovered is defined as an EXACT exacerbation meeting the Recovery definition outline above. Censored is defined as an EXACT exacerbation that began within 28 days of study termination and did not meet the Recovery definition during that

time period. Persistent Worsening is defined as an EXACT exacerbation that never meets the Recovery criteria, i.e., the patient's EXACT scores never meet the Recovery definition. All analyses including Recovery should be based on resolved events only, unless otherwise specified.

**New Event (Stabilisation Phase)**

Score increases consistent with Onset and occurring any time after the 7th day of the Recovery period are counted as a new event. To identify a new exacerbation, use the last available Baseline value. The reset Baseline value ($Baseline_{RX}$) is used if a patient's Baseline was re-established prior to the EXACT exacerbation; otherwise the original Baseline value from Stabilisation Phase (i.e. mean EXACT score during the first 7 days of the Stabilisation Phase (Week 3; Days 15-21)) is used. If no new event is experienced during the 4 week period post-Recovery, Baseline is reset in the manner described previously. There may be a new event beginning on the day after the day of recovery, but not on the day of recovery.

**Duration (Stabilisation Phase)**

Duration is the length of time in days from Onset to Recovery. Duration is calculated as the difference, in days, between the day of Onset ($Day_1$) and the day of Recovery ($Day_R$). The day of Recovery ($Day_R$) is not included in calculating Duration days.

**Event Severity (Stabilisation Phase)**

Severity is the highest EXACT Total score of the observation period from Onset ($Day_1$) to Recovery ($Day_R$), not using the 3-day Rolling Average. For patients who do not recover severity is the highest EXACT Total score of the observation period.

**Table 1: Annotated EXACT for Raw Score Assignment**

The following annotates the raw item-level score values associated with each text response for the EXACT items.

| | |
|---|---|
| 1. Did your chest feel congested today? | 0. Not at all |
| | 1. Slightly |
| | 2. Moderately |
| | 3. Severely |
| | 4. Extremely |
| 2. How often did you cough today? | 0. Not at all |
| | 1. Rarely |
| | 2. Occasionally |
| | 3. Frequently |
| | 4. Almost constantly |
| 3. How much mucus (phlegm) did you bring up when coughing today? | 0. None at all |
| | 1. A little |
| | 1. Some |
| | 2. A great deal |
| | 3. A very great deal |
| | *NOTE: Score "A little" and "Some" the same.* |
| 4. How difficult was it to bring up mucus (phlegm) today? | 0. Not at all |
| | 1. Slightly |
| | 2. Moderately |
| | 3. Quite a bit |
| | 4. Extremely |
| 5. Did you have chest discomfort today? | 0. Not at all |
| | 1. Slight |
| | 2. Moderate |
| | 3. Severe |
| | 4. Extreme |
| 6. Did your chest feel tight today? | 0. Not at all |
| | 1. Slightly |
| | 2. Moderately |
| | 3. Severely |
| | 4. Extremely |

| | |
|---|---|
| 7. Were you breathless today? | 0. Not at all |
| | 1. Slightly |
| | 2. Moderately |
| | 3. Severely |
| | 4. Extremely |
| 8. Describe how breathless you were today: | 0. Unaware of breathlessness |
| | 1. Breathless during strenuous activity |
| | 2. Breathless during light activity |
| | 3. Breathless when washing or dressing |
| | 3. Present when resting |
| | *NOTE: Score "Breathless when washing or dressing" and "Present when resting" the same.* |
| 9. Were you short of breath today when performing your usual personal care activities like washing or dressing? | 0. Not at all |
| | 1. Slightly |
| | 2. Moderately |
| | 3. Severely |
| | 3. Extremely |
| | 4. Too breathless to do these |
| | *NOTE: Score "Severely" and "Extremely" the same.* |
| 10. Were you short of breath today when performing your usual indoor activities like cleaning or household work? | 0. Not at all |
| | 1. Slightly |
| | 2. Moderately |
| | 3. Severely |
| | 3. Extremely |
| | 3. Too breathless to do these |
| | *NOTE: Score "Severely," "Extremely," and "Too breathless to do these" the same.* |
| 11. Were you short of breath today when performing your usual activities outside the home such as yard work or errands? | 0. Not at all |
| | 1. Slightly |
| | 2. Moderately |
| | 3. Severely |
| | 3. Extremely |
| | 3. Too breathless to do these |
| | *NOTE: Score "Severely," "Extremely", and "Too breathless to do these" the same.* |

| | |
|---|---|
| 12. Were you tired or weak today? | 0. Not at all |
| | 1. Slightly |
| | 2. Moderately |
| | 3. Severely |
| | 4. Extremely |
| 13. Last night, was your sleep disturbed? | 0. Not at all |
| | 1. Slightly |
| | 2. Moderately |
| | 3. Severely |
| | 4. Extremely |
| 14. How scared or worried were you about your lung problems today? | 0. Not at all |
| | 1. Slightly |
| | 2. Moderately |
| | 3. Severely |
| | 3. Extremely |
| | *NOTE: Score "Severely" and "Extremely" the same.* |

**Table 2: Raw Summed Score to Scale Score Conversion Table for EXACT Total Score**

| Raw Summed Score | EXACT® Total Score | Raw Summed Score (continued) | EXACT® Total Score |
|---|---|---|---|
| 0 | 0 | 26 | 50 |
| 1 | 8 | 27 | 51 |
| 2 | 13 | 28 | 52 |
| 3 | 17 | 29 | 53 |
| 4 | 20 | 30 | 54 |
| 5 | 23 | 31 | 55 |
| 6 | 25 | 32 | 57 |
| 7 | 27 | 33 | 58 |
| 8 | 28 | 34 | 59 |
| 9 | 30 | 35 | 60 |
| 10 | 31 | 36 | 61 |
| 11 | 33 | 37 | 63 |
| 12 | 34 | 38 | 64 |
| 13 | 36 | 39 | 65 |
| 14 | 37 | 40 | 67 |
| 15 | 38 | 41 | 68 |
| 16 | 39 | 42 | 70 |
| 17 | 40 | 43 | 72 |
| 18 | 41 | 44 | 73 |
| 19 | 42 | 45 | 75 |
| 20 | 43 | 46 | 77 |
| 21 | 44 | 47 | 80 |
| 22 | 46 | 48 | 83 |
| 23 | 47 | 49 | 87 |
| 24 | 48 | 50 | 92 |
| 25 | 49 | 51 | 100 |

This conversion table converts raw summed scores to a 0 to 100 scale, for ease of interpretation.

**Table 3: Raw Summed Score to Scale Score Conversion Table for EXACT Domains**

| Domain Raw Summed Score[a] | Breathlessness Domain Score | Cough & Sputum Domain Score | Chest Symptoms Domain Score |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 1 | 11 | 13 | 12 |
| 2 | 19 | 25 | 23 |
| 3 | 25 | 39 | 31 |
| 4 | 30 | 56 | 38 |
| 5 | 34 | 72 | 45 |
| 6 | 38 | 86 | 52 |
| 7 | 42 | 100 | 58 |
| 8 | 45 | | 65 |
| 9 | 48 | | 72 |
| 10 | 52 | | 79 |
| 11 | 56 | | 88 |
| 12 | 60 | | 100 |
| 13 | 65 | | |
| 14 | 71 | | |
| 15 | 78 | | |
| 16 | 87 | | |
| 17 | 100 | | |

[a]The maximum score for the chest symptoms domain is 12. The maximum score for the Cough & Sputum domain is 7.

**Table 4: SAS Coding Instructions for Computing Daily Scores**

The following example assumes all original item responses are coded as 0, 1, 2, 3, 4, etc. on the data collection forms or electronic data capture system, ordered from least severe to most severe. In this case, only items 3, 8, 9, 10, 11, and 14 need to be recoded to form item-level scores. If the original codes begin with 1 for least severe (e.g., 1, 2, 3, 4, 5 for question 1), then the codes must be shifted to a 0 starting point for all items before these SAS statements can be used.

| | |
|---|---|
| 1. Assign raw score values associated with each response category for the EXACT® items: | if q3 in (1,2) then q3=1;<br>else if q3 in (3) then q3=2;<br>else if q3 in (4) then q3=3;<br>if q8 in (3,4) then q8=3;<br>if q9 in (3,4) then q9=3;<br>else if q9 in (5) then q9=4;<br>if q10 in (3,4,5) then q10=3;<br>if q11 in (3,4,5) then q11=3;<br>if q14 in (3,4) then q14=3;<br>rawsum=sum (of q1-q14);<br>breathlesssum=sum (of q7-q11);<br>coughsum=sum (of q2 q3);<br>chestsum=sum (of q1 q5 q6); |
| 2. Assign the EXACT® Total score for each raw summed score: | select (rawsum);<br>when(0) Exact_total=0;<br>when(1) Exact_total=8;<br>when(2) Exact_total=13;<br>when(3) Exact_total=17;<br>when(4) Exact_total=20;<br>when(5) Exact_total=23;<br>when(6) Exact_total=25;<br>when(7) Exact total=27;<br>when(8) Exact_total=28;<br>when(9) Exact_total=30;<br>when(10) Exact_total=31;<br>when(11) Exact_total=33;<br>when(12) Exact_total=34;<br>when(13) Exact_total=36;<br>when(14) Exact_total=37;<br>when(15) Exact_total=38;<br>when(16) Exact total=39;<br>when(17) Exact_total=40;<br>when(18) Exact_total=41;<br>when(19) Exact_total=42;<br>when(20) Exact_total=43;<br>when(21) Exact_total=44;<br>when(22) Exact_total=46;<br>when(23) Exact_total=47;<br>when(24) Exact_total=48;<br>when(25) Exact total=49;<br>when(26) Exact_total=50;<br>when(27) Exact_total=51;<br>when(28) Exact_total=52; |

| | |
|---|---|
| | when(29) Exact_total=53;<br>when(30) Exact_total=54;<br>when(31) Exact_total=55;<br>when(32) Exact_total=57;<br>when(33) Exact_total=58;<br>when(34) Exact_total=59;<br>when(35) Exact_total=60;<br>when(36) Exact total=61;<br>when(37) Exact_total=63;<br>when(38) Exact_total=64;<br>when(39) Exact_total=65;<br>when(40) Exact_total=67;<br>when(41) Exact_total=68;<br>when(42) Exact_total=70;<br>when(43) Exact_total=72;<br>when(44) Exact_total=73;<br>when(45) Exact total=75;<br>when(46) Exact_total=77;<br>when(47) Exact_total=80;<br>when(48) Exact_total=83;<br>when(49) Exact_total=87;<br>when(50) Exact_total=92;<br>when(51) Exact_total=100;<br>otherwise; |
| 3. Assign the Breathlessness domain score for each domain raw summed score: | select (breathlesssum);<br>when(0) Breathlessness=0;<br>when(1) Breathlessness=11;<br>when(2) Breathlessness=19;<br>when(3) Breathlessness=25;<br>when(4) Breathlessness=30;<br>when(5) Breathlessness=34;<br>when(6) Breathlessness=38;<br>when(7) Breathlessness=42;<br>when(8) Breathlessness=45;<br>when(9) Breathlessness=48;<br>when(10) Breathlessness=52;<br>when(11) Breathlessness=56;<br>when(12) Breathlessness=60;<br>when(13) Breathlessness=65;<br>when(14) Breathlessness=71;<br>when(15) Breathlessness=78;<br>when(16) Breathlessness=87;<br>when(17) Breathlessness=100; |
| 4. Assign the Cough & Sputum domain score for each domain raw summed score: | select (coughsum);<br>when(0) Coughsputum=0;<br>when(1) Coughsputum=13;<br>when(2) Coughsputum=25;<br>when(3) Coughsputum=39;<br>when(4) Coughsputum=56;<br>when(5) Coughsputum=72;<br>when(6) Coughsputum=86;<br>when(7) Coughsputum=100; |

| | |
|---|---|
| 5. Assign the Chest Symptom domain score for each domain raw summed score: | select (chestsum);<br>when(**0**) Chestsymptom=**0**;<br>when(**1**) Chestsymptom=**12**;<br>when(**2**) Chestsymptom=**23**;<br>when(**3**) Chestsymptom=**31**;<br>when(**4**) Chestsymptom=**38**;<br>when(**5**) Chestsymptom=**45**;<br>when(**6**) Chestsymptom=**52**;<br>when(**7**) Chestsymptom=**58**;<br>when(**8**) Chestsymptom=**65**;<br>when(**9**) Chestsymptom=**72**;<br>when(**10**) Chestsymptom=**79**;<br>when(**11**) Chestsymptom=**88**;<br>when(**12**) Chestsymptom=**100**; |

## Appendix D – Chronic Respiratory Questionnaire (CRQ)

**[READ TO RESPONDENT]**

i. This questionnaire is designed to find out how you have been feeling during the last 2 weeks.

ii. In the first section, you will be asked to answer questions about activities, which make some people feel short of breath. In the next section, you will be asked about your mood and how you have been feeling.

iii. Remember, there are no right or wrong answers.

iv. I would now like you to describe how much shortness of breath you have experienced during the last 2 weeks while doing activities, which make some people feel short of breath. When you are answering the questions about how short of breath you have been, please indicate if you have not done an activity during the last two weeks.

**[FOR ALL SUBSEQUENT QUESTIONS, ENSURE THE RESPONDENT HAS THE APPROPRIATE RESPONSE CARD IN FRONT OF THEM BEFORE STARTING QUESTION]**

| | |
|---|---|
| 1. Please indicate how much shortness of breath you have had during the last 2 weeks while feeling **emotional such as angry or upset** by choosing one of the following options from the card in front of you. **[GREEN CARD]** | EXTREMELY SHORT OF BREATH ☐<br>VERY SHORT OF BREATH ☐<br>QUITE A BIT SHORT OF BREATH ☐<br>MODERATE SHORTNESS OF BREATH ☐<br>SOME SHORTNESS OF BREATH ☐<br>A LITTLE SHORTNESS OF BREATH ☐<br>NOT AT ALL SHORT OF BREATH ☐<br>NOT DONE ☐ |
| 2. Please indicate how much shortness of breath you have had during the last 2 weeks while **taking care of your basic needs (such as bathing, showering, eating or dressing)** by choosing one of the following options from the card in front of you. **[GREEN CARD]** | EXTREMELY SHORT OF BREATH ☐<br>VERY SHORT OF BREATH ☐<br>QUITE A BIT SHORT OF BREATH ☐<br>MODERATE SHORTNESS OF BREATH ☐<br>SOME SHORTNESS OF BREATH ☐<br>A LITTLE SHORTNESS OF BREATH ☐<br>NOT AT ALL SHORT OF BREATH ☐<br>NOT DONE ☐ |

| | |
|---|---|
| 3. Please indicate how much shortness of breath you have had during the last 2 weeks while **walking** by choosing one of the following options from the card in front of you. **[GREEN CARD]** | EXTREMELY SHORT OF BREATH ☐<br>VERY SHORT OF BREATH ☐<br>QUITE A BIT SHORT OF BREATH ☐<br>MODERATE SHORTNESS OF BREATH ☐<br>SOME SHORTNESS OF BREATH ☐<br>A LITTLE SHORTNESS OF BREATH ☐<br>NOT AT ALL SHORT OF BREATH ☐<br>NOT DONE ☐ |
| 4. Please indicate how much shortness of breath you have had during the last 2 weeks while **performing chores (such as housework, shopping, groceries)** by choosing one of the following options from the card in front of you. **[GREEN CARD]** | EXTREMELY SHORT OF BREATH ☐<br>VERY SHORT OF BREATH ☐<br>QUITE A BIT SHORT OF BREATH ☐<br>MODERATE SHORTNESS OF BREATH ☐<br>SOME SHORTNESS OF BREATH ☐<br>A LITTLE SHORTNESS OF BREATH ☐<br>NOT AT ALL SHORT OF BREATH ☐<br>NOT DONE ☐ |
| 5. Please indicate how much shortness of breath you have had during the last 2 weeks while **participating in social activities** by choosing one of the following options from the card in front of you.**[GREEN CARD]** | EXTREMELY SHORT OF BREATH ☐<br>VERY SHORT OF BREATH ☐<br>QUITE A BIT SHORT OF BREATH ☐<br>MODERATE SHORTNESS OF BREATH ☐<br>SOME SHORTNESS OF BREATH ☐<br>A LITTLE SHORTNESS OF BREATH ☐<br>NOT AT ALL SHORT OF BREATH ☐<br>NOT DONE ☐ |
| 6. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient? Please indicate how much of the time you have felt frustrated or impatient by choosing one of the following options from the card in front of you. **[BLUE CARD]** | ALL OF THE TIME ☐<br>MOST OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>HARDLY ANY OF THE TIME ☐<br>NONE OF THE TIME ☐ |

| | |
|---|---|
| 7. How often during the last 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath? Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by choosing one of the following options from the card in front of you.**[BLUE CARD]** | ALL OF THE TIME ☐<br>MOST OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>HARDLY ANY OF THE TIME ☐<br>NONE OF THE TIME ☐ |
| 8. What about fatigue? How tired have you felt over the last 2 weeks? Please indicate how tired you have felt over the last 2 weeks by choosing one of the following options from the card in front of you.**[ORANGE CARD]** | EXTREMELY TIRED ☐<br>VERY TIRED ☐<br>QUITE A BIT OF TIREDNESS ☐<br>MODERATELY TIRED ☐<br>SOMEWHAT TIRED ☐<br>A LITTLE TIRED ☐<br>NOT AT ALL TIRED ☐ |
| 9. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing? Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by choosing one of the following options from the card in front of you. **[BLUE CARD]** | ALL OF THE TIME ☐<br>MOST OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>HARDLY ANY OF THE TIME ☐<br>NONE OF THE TIME ☐ |
| 10. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness? Please indicate how much of the time you felt very confident and sure that you could deal with your illness by choosing one of the following options from the card in front of you. **[YELLOW CARD]** | NONE OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>MOST OF THE TIME ☐<br>ALMOST ALL OF THE TIME ☐<br>ALL OF THE TIME ☐ |
| 11. How much energy have you had in the last 2 weeks? Please indicate how much energy you have had by choosing one of the following options from the card in front of you. **[PINK CARD]** | NO ENERGY ☐<br>A LITTLE ENERGY ☐<br>SOME ENERGY ☐<br>MODERATELY ENERGETIC ☐<br>QUITE A BIT OF ENERGY ☐<br>VERY ENERGETIC ☐<br>FULL OF ENERGY ☐ |

| | |
|---|---|
| 12. In general, how much of the time did you feel upset, worried or depressed during the last 2 weeks?<br>Please indicate how much of the time you felt upset, worried or depressed during the past 2 weeks<br>by<br>choosing one of the following options from the card in front of you. **[BLUE CARD]** | ALL OF THE TIME ☐<br>MOST OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>HARDLY ANY OF THE TIME ☐<br>NONE OF THE TIME ☐ |
| 13. How often during the last 2 weeks did you feel you had complete control of your breathing problems?<br>Please indicate how often you felt you had complete control of your breathing problems by choosing<br>one of the following options from the card in front of you. **[YELLOW CARD]** | NONE OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>MOST OF THE TIME ☐<br>ALMOST ALL OF THE TIME ☐<br>ALL OF THE TIME ☐ |
| 14. How much of the time during the last 2 weeks did you feel relaxed and free of tension? Please indicate how much of the time you felt relaxed and free of tension by choosing one of the following options from the card in front of you. **[YELLOW CARD]** | NONE OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>MOST OF THE TIME ☐<br>ALMOST ALL OF THE TIME ☐<br>ALL OF THE TIME ☐ |
| 15. How often during the last 2 weeks have you felt low in energy? Please indicate how often during<br>the<br>last 2 weeks you felt low in energy by choosing one of the following options from the card in front<br>of you. **[BLUE CARD]** | ALL OF THE TIME ☐<br>MOST OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>HARDLY ANY OF THE TIME ☐<br>NONE OF THE TIME ☐ |
| 16. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?<br>Please<br>indicate how often during the last 2 weeks you felt discouraged or down in the dumps by choosing<br>one<br>of the following options from the card in front of you. **[BLUE CARD]** | ALL OF THE TIME ☐<br>MOST OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>HARDLY ANY OF THE TIME ☐<br>NONE OF THE TIME ☐ |

| | |
|---|---|
| 17. How often during the last 2 weeks have you felt worn out or sluggish? Please indicate how much of the time you felt worn out or sluggish by choosing one of the following options from the card in front of you. **[BLUE CARD]** | ALL OF THE TIME ☐<br>MOST OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>HARDLY ANY OF THE TIME ☐<br>NONE OF THE TIME ☐ |
| 18. How happy, satisfied, or pleased have you been with your personal life during the last 2 weeks? Please indicate how happy, satisfied or pleased you have been by choosing one of the following options from the card in front of you. **[GREY CARD]** | VERY DISSATISFIED, UNHAPPY MOST OF THE TIME ☐<br>GENERALLY DISSATISFIED, UNHAPPY ☐<br>SOMEWHAT DISSATISFIED, UNHAPPY ☐<br>GENERALLY SATISFIED, PLEASED ☐<br>HAPPY MOST OF THE TIME ☐<br>VERY HAPPY MOST OF THE TIME ☐<br>EXTREMELY HAPPY, COULD NOT BE MORE SATISFIED OR PLEASED ☐ |
| 19. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath? Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by choosing one of the following options from the card in front of you. **[BLUE CARD]** | ALL OF THE TIME ☐<br>MOST OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>HARDLY ANY OF THE TIME ☐<br>NONE OF THE TIME ☐ |
| 20. In general, how often during the last 2 weeks have you felt restless, tense or uptight? Please indicate how often you felt restless tense, or uptight by choosing one of the following options from the card in front of you. **[BLUE CARD]** | ALL OF THE TIME ☐<br>MOST OF THE TIME ☐<br>A GOOD BIT OF THE TIME ☐<br>SOME OF THE TIME ☐<br>A LITTLE OF THE TIME ☐<br>HARDLY ANY OF THE TIME ☐<br>NONE OF THE TIME ☐ |

## Appendix E – Body mass index, airflow Obstruction, Dyspnoea and Exercise index (BODE)

### BODE Index for COPD

**Scoring the BODE Index**

| | 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| $FEV_1$% pred | ≥65 | 50-64 | 36-49 | ≤35 |
| 6MWD (m) | ≥350 | 250-349 | 150-249 | ≤149 |
| MMRC | 0-1 | 2 | 3 | 4 |
| BMI ($kg.m^{-2}$) | >21 | ≤21 | | |

Total BODE Index score = 0 to 10 units

(FEV1% pred = predicted amount as a percentage of the forced expiratory lung volume in one second; 6MWD = six minute walking distance; MMRC = modified medical research council dyspnea scale; BMI = body mass index)

| Modified MRC Dyspnoea Scale | |
|---|---|
| 0 | Breathless only with strenuous exercise |
| 1 | Short of breath when hurrying on the level or walking up a slight hill |
| 2 | Slower than most 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 | Stop for breath after walking about 100 meters or after a few minutes at my own pace on the level |
| 4 | Too breathless to leave the house or I am breathless when dressing |

## Appendix F – Algorithms/SAS Reference Codes

- **Calculation of adjusted means (least squares means):**

The approach described below will ensure that the least squares means calculated by SAS will be based on:

- coefficients for classification effects (i.e., the effects of categorical covariates) proportional to the margins observed in the group of patients analysed;
- effects of quantitative covariates set equal to their mean values in the group of patients analysed.

The analysis is based on the following steps:

1. generate a dataset by selecting:
   - in case of repeated post-randomisation measurements (e.g. FEV1 at each visit, analysed using a linear mixed model for repeated measures): all the post-randomisation records for patients with at least one available and valid post-randomisation measurement and no missing covariates;
   - in case of single post-randomisation measurement (e.g. number of COPD exacerbations during the Stabilisation Phase based on EXACT-PRO, analysed using a negative binomial model): all the patients with available and valid response and no missing covariates;
2. in case of repeated post-randomisation measurements, add to the dataset generated in step 1 the records for missing post-randomisation visits of the patients included in the dataset. In the added records the value of the response variable will be missing, but the full information on covariates has to be included;
3. use the dataset obtained as the input dataset for the MIXED or the GENMOD procedure, specifying the following options in the LSMEANS statement:
   - in case of repeated post-randomisation measurements: OM AT MEANS;
   - in case of single post-randomisation measurement: OM.

Example: analysis of change from baseline (Visit 1) at all visits (Visits 2 to 7) based on a mixed model for repeated measures including the effects of treatment, visit (categorical variable), treatment by visit interaction, baseline and another covariate.

Original dataset (X = available value; . = missing or invalid value):

| Patient | Treatment | Covariate | Baseline | Visit | Change from baseline |
|---|---|---|---|---|---|
| 1 | A | X | X | 1 | . |
| 1 | A | X | X | 2 | . |
| 1 | A | X | X | 3 | X |
| 1 | A | X | X | 4 | X |
| 1 | A | X | X | 5 | X |
| 1 | A | X | X | 6 | X |
| 1 | A | X | X | 7 | . |
| 2 | B | X | X | 1 | . |
| 2 | B | X | X | 2 | . |
| 2 | B | X | X | 3 | X |
| 3 | C | X | X | 1 | . |
| 3 | C | X | X | 2 | . |
| 3 | C | X | X | 3 | X |
| 3 | C | X | X | 4 | . |
| 3 | C | X | X | 5 | X |
| 3 | C | X | X | 6 | . |
| 3 | C | X | X | 7 | X |
| 4 | B | X | X | 1 | . |
| 4 | B | X | X | 2 | . |
| 5 | A | . | X | 1 | . |
| 5 | A | . | X | 2 | . |
| 5 | A | . | X | 3 | X |

Step 1 (visit 1 not selected since pre-treatment, patient 4 not selected due to missing post-randomisation measurements, patient 5 not selected due to missing covariate):

| Patient | Treatment | Covariate | Baseline | Visit | Change from baseline |
|---|---|---|---|---|---|
| 1 | A | X | X | 2 | . |
| 1 | A | X | X | 3 | X |
| 1 | A | X | X | 4 | X |
| 1 | A | X | X | 5 | X |
| 1 | A | X | X | 6 | X |
| 1 | A | X | X | 7 | . |
| 2 | B | X | X | 2 | . |
| 2 | B | X | X | 3 | X |
| 3 | C | X | X | 2 | . |
| 3 | C | X | X | 3 | X |
| 3 | C | X | X | 4 | . |
| 3 | C | X | X | 5 | X |
| 3 | C | X | X | 6 | . |
| 3 | C | X | X | 7 | X |

Step 2 (added records in *italic* and **bold**):

| Patient | Treatment | Covariate | Baseline | Visit | Change from baseline |
|---|---|---|---|---|---|
| 1 | A | X | X | 2 | . |
| 1 | A | X | X | 3 | X |
| 1 | A | X | X | 4 | X |
| 1 | A | X | X | 5 | X |
| 1 | A | X | X | 6 | X |
| 1 | A | X | X | 7 | . |
| 2 | B | X | X | 2 | . |
| 2 | B | X | X | 3 | X |
| ***2*** | ***B*** | ***X*** | ***X*** | ***4*** | **.** |
| ***2*** | ***B*** | ***X*** | ***X*** | ***5*** | **.** |
| ***2*** | ***B*** | ***X*** | ***X*** | ***6*** | **.** |
| ***2*** | ***B*** | ***X*** | ***X*** | ***7*** | **.** |
| 3 | C | X | X | 2 | . |
| 3 | C | X | X | 3 | X |
| 3 | C | X | X | 4 | . |
| 3 | C | X | X | 5 | X |
| 3 | C | X | X | 6 | . |
| 3 | C | X | X | 7 | X |

- **Tables that require Chi-Square test with continuity correction:**

*PROC FREQ DATA = <dataset name>;*
*TABLES <outcome variable>*<predictor variable> / CHISQ OUT=<output dataset name>*
*OUTPUT OUT=stats;*
*RUN;*

**Notes**:
- In case the assumption of Chi-square test is not met (e.g. expected cell frequencies < 5), a Fisher's exact test will be carried out. The SAS code is similar as above but with "FISHER" option in the "TABLES" statement above.

- **Tables that require One-way ANOVA test:**

*PROC ANOVA DATA = <dataset name>;*
*CLASS <predictor variable>;*
*MODEL <outcome variable> = <predictor variable>;*
*RUN;*

**Notes**:
- Should the normality assumptions for the outcome variable not be met (the skewness and kurtosis measurements will be considered as supportive indicators), the relationship between the outcome variable and the predictor variable will be tested using the non-parametric approach of Kruskal-Wallis test (or Wilcoxon Rank-Sum test for two groups). The SAS code used to implement this test will be:

*PROC NPAR1WAY DATA = <dataset name> WILCOXON;*
*CLASS <predictor variable>;*
*VAR <outcome variable>;*
*RUN;*

- **Tables that require Kaplan-Meier estimates and log-rank test:**

*PROC LIFETEST data=dataset timelist=(0 t1 t2 t3 t4 t5 … EoS) alpha=.05 outsurv=estim reduceout;*
*TIME time*event(0);*
*STRATA trt;*
*RUN;*

**Notes**:
- Time represents the time to event or time to censoring;
- Event represents the censoring indicator (0 = censored);
- Trt represents the treatment group;
- EoS should be replaced by the last time to event >26 weeks (if any).