EXCALIBUR

Statistical Analysis Plan

Trial name:	EXCALIBUR
Trial registration number:	ISRCTN26614726
Protocol title and version number:	V6 23Aug2022
SAP version number:	1.0
SAP date:	09 November 2022

To be approved and reviewed by:

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List of Abbreviations

Abbreviation		Abbreviation	
ADR	Adverse Drug Reaction	ISF	Investigator Site File
AE	Adverse Event	ISRCTN	International Standard Randomised Controlled Trial Number
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease	MHRA	Medicines and Healthcare products Regulatory Agency
AR	Adverse Reaction	NICE	National Institute for Clinical Excellence
CI	Chief Investigator	PI	Principal Investigator
COPD	Chronic Obstructive Pulmonary Disease	PIS	Patient Information Sheet
CRF	Case Report Form	PPI	Public and Patient Involvement
CRP	C-Reactive Protein	RA	Research Assistant
CTA	Clinical Trial Authorisation	REC	Research Ethics Committee
CTCAE	Common Terminology Criteria for Adverse Events	SAE	Serious Adverse Event
DHSC	Department of Health and Social Care	SAP	Statistical Analysis Plan
DMEC	Data Monitoring and Ethics Committee	SAR	Serious Adverse Reaction
DMP	Data Management Plan	SFJD	Shufeng Jiedu
eCRF	Electronic Case Report Form	SmPC	Summary of Product Characteristics
GCP	Good Clinical Practice	SCTU	Southampton Clinical Trials Unit
GOLD	Global Initiative for Chronic Obstructive Lung Disease	SUSAR	Suspected Unexpected Serious Adverse Reaction
GP	General Practitioner	TMF	Trial Master File
HCA	Health Care Assistant	TMG	Trial Management Group
IB	Investigator Brochure	TSC	Trial Steering Committee
ICH	International Conference on Harmonization	UAR	Unexpected Adverse Reaction

1 Introduction

1.1 Purpose of SAP

This statistical analysis plan (SAP) describes in detail the methods that will be used to analyse the data collected as part of the EXCALIBUR trial. This will form the basis of the final trial publication. The final analysis will follow the SAP to ensure that the analyses are conducted in a scientifically valid manner and to avoid post hoc decisions which may affect the interpretation of the statistical analysis. Any deviations from the SAP will be detailed in the final report.

1.2 Trial Personnel

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1.3 Trial background and rationale (short synopsis)

Chronic obstructive pulmonary disease (COPD) is a serious threat to human health, as it is the third most serious cause of death in China and worldwide (Quaderi and Hurst, 2018). There are estimated to be 3 million patients in the UK who have COPD (and up to 65 million worldwide and 25 million in China), and current global projections indicate that COPD is set to increase in line with ageing populations and a rise in smoking. In addition to being a leading cause of death worldwide, COPD is a substantial burden to those it affects. Due to the nature of COPD as a chronic disease, patients typically have an impaired quality of life and suffer from disability and impaired motility.

Patients with COPD are prone to sudden worsenings know as "Acute exacerbations" (AECOPD) and these can be caused by bacterial infections, viral infections and environmental triggers. AECOPD are a major reason for healthcare consultations in primary care, hospital admissions, deterioration in function, and mortality in patients with COPD. In the UK, COPD is estimated to result in around 1.4 million GP consultations and 130,000

emergency hospital admissions each year, with a direct cost to the NHS of between £810 - £930 million each year (NICE guideline on managing COPD). Over 70% of patients presenting with AECOPD in UK primary care are currently prescribed antibiotics (Butler et al, 2019), despite the majority not being caused by a bacterial exacerbation. In a recent UK trial (Butler et al, 2019) only 44% of patients providing a baseline sputum sample had a bacterial pathogen isolated (unpublished data), and in a study in 11 hospitals in Beijing only 34% had pathogenic bacteria. Antimicrobial treatment in patients with COPD can reduce the infecting load without entirely eradicating organisms in the airways, leading to an increased risk of resistant bacteria (Miravitlles M, 2002).

AECOPD also account for the largest proportion of costs associated with COPD, as they often require hospitalisation and further treatment. Therefore, exacerbations of COPD generate high healthcare costs and thus COPD is a substantial socioeconomic burden in China, as well as in other middle-income countries and in the UK. Further economic impact is driven by loss of working days due to illness. Therefore, finding effective treatments for COPD exacerbations is a priority to reduce the cost for health systems and the economy as a whole (Feenstra et al. 2001).

In this project we will examine the use of a patented traditional Chinese medicine (TCM) called "Shufeng Jiedu" (SFJD) in a cohort of patients experiencing an AECOPD. SFJD is already on the market in China for treatment of respiratory infections, though not specifically for AECOPD. SFJD is a standardised combination of eight herbs, all of which have been used in traditional Chinese medicine for centuries, and all of which are available in the UK through consultation with a herbal practitioner (not restricted by the Medicines and Healthcare products Regulatory Agency (MHRA)). Preliminary research in China has suggested that use of SFJD, when given together with antibiotics to patients with AECOPD, can reduce risk of treatment failure, and duration of hospital admission (Xin Yao, 2017). A systematic review performed by the research team suggests that SFJD plus usual care is associated with a significant reduction in treatment failure, from 20.1% to 8.3% (11 trials; 815 patients; relative risk 0.43, 95% confidence interval [CI] 0.30 to 0.62; low certainty) and duration of hospital admission (2 trials; 79 patients; mean difference -4.35 days, 95% CI -5.28 to -3.43 days) when compared with usual care (results not published). The review found no evidence of a significant difference in adverse events between the two groups.

We hypothesise that SFJD will improve symptoms in people with AECOPD, and will therefore reduce the necessity for antibiotics, the risk and duration of admission to hospital, and the risk of relapse. This trial will be a feasibility study in patients treated for AECOPD in primary care in the UK, in preparation for a full trial to assess whether adding SFJD to standard treatment will enable patients to improve faster, thus reducing the necessity for antibiotics and reducing their risk of admission to hospital. If successful, this would pave the way for a full-scale clinical trial in the UK. The addition of SFJD to antibiotics has the potential to significantly reduce healthcare costs associated with COPD and to reduce the risk of development of antimicrobial resistance, by reducing the number of antibiotic prescriptions and reducing the risk and duration of hospital admission.

1.4 Objectives

The overarching objective of this mixed methods study is to determine the feasibility of conducting a fully powered trial of SFJD in addition to best current practice for AECOPD in UK primary care. Specific feasibility objectives are detailed below.

Recruitment process and resources:

- Eligibility: Proportion of patients on the COPD register who present with AECOPD
- Eligibility: Proportion of AECOPD-presenting patients eligible and ineligible (plus reasons) for the trial
- Recruitment/Randomisation: Proportion of eligible patients recruited
- Recruitment: Rate of recruitment in the UK primary care setting
- Retention: Across the duration of the trial

Intervention management and procedures:

- Intervention compliance, including feasibility and acceptability of the intervention

- Feasibility and acceptability of the trial procedures
- Distribution and access to product for the trial duration
- Determine issues around safety and ADR reporting
- Determine the acceptability of the diary and patient's willingness to complete them
- Effectiveness of blinding

Outcome measures

- Distribution of patient reported outcome measure scores
- Antibiotic prescribing and use

1.5 Definition of endpoints

1.5.1 Feasibility endpoints

The following feasibility endpoints will be assessed in order to meet the objectives above:

- Number and proportion of patients on the COPD register who present with AECOPD.
- Proportion of patients presenting with AECOPD that are eligible and ineligible (plus reasons) for the trial
- Proportion of eligible patients recruited
- Recruitment rate per site per month open
- Compliance with medication according to diary data and returned medication
- Average no. of capsules taken per day per patient
- Duration of treatment per patient
- % of patients correctly guessing treatment/placebo allocation and reasons why.
- % of patients returning trial diaries
- % of diary completion
- % of patients who took antibiotics in each group
- % of patients given immediate and delayed antibiotic prescriptions

1.5.2 Qualitative endpoints

Information from qualitative interviews will be analysed separately.

1.6 Analysis principles

All analyses will be reported according to CONSORT 2010, CONSORT herbal extension checklist (Gagnier et al. 2006) and Southampton Clinical Trials Unit (SCTU) standard operating procedure (SOP) on planning, implementing and reporting statistical analyses (CTU/SOP/5058).

2 Design considerations

2.1 Description of trial design

This is a double-blind, randomised placebo-controlled feasibility trial, incorporating a nested qualitative study. This study will be reported following the CONSORT herbal extension checklist (Gagnier et al. 2006), with the nested qualitative elements being reported using the COREQ checklist.

Eligible patients will be randomised to receiving SFJD capsules or placebo capsules, in addition to the best current practice based on the NICE guidance for managing an AECOPD.

Whether they are participating in the feasibility study or not, eligible AECOPD patients will be invited to participate in semi-structured interviews conducted by phone, with some pre-set open-ended questions and probes to direct the interviews.

2.2 Trial power and sample size

The sample size for this trial will be 80 patients (40 per arm). Patients will receive either SFJD or placebo capsules in 1:1 allocation ratio.

As this is a feasibility trial, no formal sample size calculation was carried out. Using a 95% confidence interval approach and an expected proportion of 50% (to give the worst-case scenario) it can be shown that this sample size allows us to predict the recruitment rate to within 13% [IBM SPSS Statistics for Macintosh, Version 25.0].

2.3 Randomisation details

Patients who meet the eligibility criteria for the trial as determined by the inclusion and exclusion criteria and for whom written informed consent has been obtained will be allocated via 1:1 individual, random-sized block randomisation to either treatment or corresponding placebo, no stratification factors will be used.

The treatment packs will be sent to site in sets of four and each patient will receive the next available sequentially numbered patient pack at their site. This will determine their Patient (Subject) Identifier number.

The doctor or nurse allocating the patient pack and the patient will not know to which treatment arm they have been randomised. The patient pack will contain either SFJD or placebo capsules. Outcome assessors will also be blind to treatment allocation.

2.4 Timing of planned analyses

2.4.1 Interim analyses and early stopping

No interim analyses are planned and no IDMC or DMEC will be convened for EXCALIBUR.

2.4.2 Final analysis

The final analysis will be conducted at the end of the trial once all participants have ended treatment, all diaries are either returned or otherwise accounted for and verified, and external notes reviews have been completed. Patient data will be analysed and presented by arm, as well as overall, to allow comparison between the different groups in accordance with the study objectives.

3 Statistical considerations

3.1 Definition of analysis populations

3.1.1 Intention-to-treat analysis population

The ITT population includes all randomised participants, regardless of treatment compliance or the actual treatment received.

3.2 Analysis software

SAS version 9.4 or above and/or STATA version 16 or above will be used for analyses.

3.3 Methods for handling data

3.3.1 Withdrawal from trial

The participant is free to withdraw consent from the trial at any time without providing a reason. Investigators should explain to participants the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, participants who have withdrawn from trial treatment should remain in follow-up as per the trial schedule. If participants additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician. It would remain useful for the trial team to continue to collect standard follow-up data and unless the participant explicitly states otherwise, follow-up data will continue to be collected.

Details of trial discontinuation (date, reason if known) should be recorded in the eCRF and medical record.

3.3.2 Missing data

The proportion of missing data is itself a feasibility outcome and will be reported, therefore no imputation of missing or incomplete data is planned.

3.3.3 Outliers

No methods will be used to handle outliers in the data.

3.3.4 Assumption checking and alternative methods

Not applicable since no statistical comparisons or modelling will be performed.

3.3.5 Data transformations

Not applicable since no statistical comparisons or modelling will be performed.

3.4 Definition of key derived variables

Symptom resolution and length of exacerbation:

- **First day of symptom resolution (FDSR):** If the Symptom Resolution section of the Participant Diary has a final entry of “No” (indicating that the patient has no AECOPD symptoms), then the first consecutive “No” entry will be used. If the Symptom Resolution section of the Participant Diary has a final entry of “Yes” and the Diary by Recall has a resolution date after the date of last entry, then the diary by recall will be used for the first day of symptom resolution.
- **First day of symptom resolution according to Participant Diary:** If the Symptom Resolution section of the Participant Diary has a final entry of “No” then the first consecutive “No” entry will be used.

- **FDSR available from Participant Diary:** Indicator variable, "Yes" if Participant Diary has a final entry of "No" and "No" otherwise.
- **FDSR available from Diary by Recall:** Indicator variable, "Yes" if Diary By Recall has a resolution date given and "No" otherwise.
- **Difference in FDSR between Participant Diary and Diary by Recall:** Calculated as FDSR according to Participant Diary – FDSR according to Diary by Recall.
- **Days experiencing COPD exacerbation:** Calculated as date of first day of symptom resolution – date of baseline visit + no. of days experiencing AECOPD recorded at baseline.

PROMs:

- **CAT Score:** Integer score from 0-40, calculated as the sum of the 8 individual answers of 0-5. If any of the questionnaire answers is missing, then the entire score is missing.
- **EXACT-PRO score:** Calculated according to EXACT-PRO scoring manual; the answer to each question is scored according to the manual, then all individual scores are summed, and this sum is scaled to give a final score from 0 to 100. If any of the questionnaire answers is missing, then the entire score is missing.

Compliance to study medication and procedures:

NOTE: Full medication compliance is assumed as 4 capsules, 3 times a day over 14 days = 4 x 3 x 14 = 168 capsules

- **Compliance with medication:** Calculated in order of preference using the methods below based on either returned medication; if not available then from Participant Diary; and finally, if both are not available then from Diary by Recall.
- **Compliance with medication according to returned medication:** Calculated as (168 – number of capsules returned)/168.
- **Compliance with medication according to Participant Diary:** Calculated as sum of all capsules taken morning, midday and evening between day 1 and day 21 according to Trial Medication section of diary/168.
- **Compliance with medication according to Diary by Recall:** Calculated as no. of days trial medication taken for*no. of capsules taken per day according to Diary by Recall/168.
- **Capsules taken per day according to Participant Diary:** Calculated as total no. of capsules taken according to Participant Diary/no. of expected entries (3 per day) between first and last entry on which trial medication was >0, divided by 3
- **Difference in capsules taken per day according to diary and diary by recall:** Calculated as capsules taken per day according to Participant Diary – capsules taken per day according to Diary by Recall.
- **Duration of treatment according to returned medication (days):** Assuming full compliance of 12 capsules per day; calculated as (168 – no. of returned capsules)/12.
- **Duration of treatment according to Participant Diary (days):** Calculated as no. of expected medication entries between the first and last entries that are non-zero and non-missing, divided by 3.
- **Proportion of trial diary completed:** Classified as follows:
  - *Complete Diaries (2 days confirmed symptom resolution)* - defined as Participant Diary completed up to 2 days after the complete resolution of symptoms or for 28 days whichever is earliest. Symptom field must be complete for all days within that period to count as completed overall. A diary is counted as complete irrespective of whether the data was completed in the Participant Diary or was completed later via Diary by Recall.
  - *Complete Diaries (7 days confirmed symptom resolution)* - defined as Participant Diary completed up to 7 days after the complete resolution of symptoms or for 28 days whichever is earliest. Symptom field must be complete for all days within that period to count as completed overall. A diary is counted as complete irrespective of whether the data was completed in the Participant Diary or was completed later via Diary by Recall.
  - *Incomplete Diaries with useable antibiotic use data* – data on symptom resolution is unavailable or incomplete, but useable antibiotic use data is provided.

- *Incomplete Diaries with other useable endpoint data* – data on symptom resolution is unavailable or incomplete, but other useable endpoint data is provided regarding at least one of; duration of trial medication, OCS use, EXACT-PRO scores or CAT scores.
- *Incomplete Diaries with unusable endpoint data* – a diary is returned but no useable information is provided on any of the following endpoints; symptom resolution, duration of trial medication, antibiotic use, OCS use, EXACT-PRO scores or CAT scores.
- *No Diary returned* – neither Participant Diary or Diary by Recall was returned.

- **Number of days on which complete diary data was entered**: A day is considered to have complete diary data entered if the following diary sections, as applicable, have data entered; trial medication, antibiotics taken, steroids taken, symptom resolution, EXACT-PRO, CAT.
- **Duration of diary completion (days):** Calculated as maximum date on which any data is entered on any of the following diary sections; trial medication, antibiotics taken, steroids taken, symptom resolution, EXACT-PRO, CAT (excluding day 84); minus baseline date + 1.

Antibiotics & OCS Use

- **Antibiotics taken within 1 day of entering study:** Indicator variable, "Yes" if participant answers "Yes" to starting a course of antibiotics in week 1 in their Participant Diary, and the date of starting that course is not more than 1 day after their baseline visit date. Also "Yes" if they answer "Yes" to starting antibiotics within 28 days of entering study by Diary by Recall, and the date of starting antibiotics is not more than 1 day after their baseline visit date. If they do not return either their Participant Diary or provide Diary by Recall data then it is considered missing. Otherwise, variable is "No".
- **Antibiotics taken within 28 days of entering study:** Indicator variable, "Yes" if participant answers "Yes" to antibiotic use during any of weeks 1-4 in the antibiotics taken section of their Participant Diary, or if they answer "Yes" to having used ABs within 28 days by Diary by Recall. If they do not return either their Participant Diary or provide Diary by Recall then data is considered missing. Otherwise, variable is "No".
- **Antibiotics prescribed within 28 days of entering study:** Indicator variable, "Yes" if participant is prescribed antibiotics at their baseline visit or if there are any prescriptions listed in their primary care notes review within 28 days of the baseline visit. If primary care notes review is not available for the participant and no antibiotics prescribed at baseline, then data is considered missing. Otherwise, variable is "No".
- **OCS taken within 1 day of entering study:** Indicator variable, "Yes" if participant answers "Yes" to starting a course of OCS in week 1 in their Participant Diary, and the date of starting that course is not more than 1 day after their baseline visit date. If they do not complete week 1 of the steroids taken section in their Participant Diary, then data is considered missing. Otherwise, variable is "No".
- **OCS taken within 28 days of entering study:** Indicator variable, "Yes" if participant answers "Yes" to increasing or starting a course of steroids during any of weeks 1-4 in the Steroids Taken section of their Participant Diary. If they do not complete any information in the steroids taken section of their Participant Diary, then data is considered missing. Otherwise, variable is "No".

Recruitment and retention

- **Recruitment rate per 1000 registered COPD patients per month open:** Calculated as 1000 x no. of participants recruited by site/no of registered COPD patients at site/no. of months site open
- **Time from baseline to end of study:** Calculated as date of end of study – date of baseline visit + 1.
- **No of patients providing complete useable endpoint data at 28 days:** Calculated as no of patients who have completed all of the following data points at 28 days, either by diary or diary by recall; trial medication, antibiotics taken, steroids taken, symptom resolution, EXACT-PRO, CAT Questionnaire.
- **No of patients providing complete useable endpoint data at 12 weeks:** Calculated as no. of patients who have completed the following data points at 12 weeks; a complete CAT Questionnaire.

3.5 General principles for reporting and analysis

- Descriptive statistics will be presented as appropriate to the nature of the data. Baseline characteristics and other continuous variables will be summarised. For example, continuous variables will usually be summarised by the number of observations, mean, standard deviation, median (interquartile range if appropriate), minimum, and maximum. Categorical variables may be summarised by frequency counts and percentages for each category.
- For continuous data, the mean, median and IQR will generally be rounded to 1 decimal place and the standard deviation to 2 decimal places. Minimum and maximum will also be displayed to 2 decimal places. Unless otherwise stated, percentages will usually be presented to 1 decimal place.
- There will be no formal statistical comparisons between groups.

4 Planned analyses and reporting

Once the data are considered final, the database will be locked, and the final analysis will be performed on the locked database. Database lock procedures will be performed according to internal SOPs. Section 5 provides examples and suggestions for the proposed outputs (tables, figures and listings) as well as the suggested structure and content of the displays. Further displays may be added at the discretion of the CI and changes from planned analyses will be documented.

4.1 Disposition of the study population

A CONSORT diagram will be produced showing a clear account of all patients who entered the study (an example is shown at this link: http://www.consort-statement.org/consort-statement/flow-diagram/) – (See **Figure 1**).

Table 1 will display a summary of populations with the numbers included in each population and the reasons why patients weren't included. **Table 2** will display screening information by site.

Detailed recruitment information will be summarised by individual site and overall in

Table 3, including the proportion of patients on the COPD register who present to their GP practice with AECOPD and are considered for eligibility into EXCALIBUR, proportion of AECOPD-presenting patients found to be eligible and ineligible for the trial (plus reasons), proportion of eligible patients who are recruited to the trial and the number of participants recruited per site per 1000 registered patients per month open.

4.2 Protocol deviations

Major protocol deviations will be summarised in **Table 4**. This will include details on the impact on analysis populations. This listing is based on the ITT population.

4.3 Baseline and demographic characteristics

Summary statistics will be produced and presented by treatment arm and overall, to summarise subject characteristics including age, gender, ethnicity, employment and smoking history (see **Table 5**). Similarly, clinical information at baseline will be summarised including AECOPD details, vital signs, Bronko test, CAT Score and EXACT-PRO Score (see

Table 6). Relevant medical history and concomitant medication data will also be presented in

Table 7.

4.4 Feasibility endpoints

4.4.1 Compliance to trial treatment and procedures

Compliance to trial medication will be described in **Feasibility endpoint** information
Table 8, as measured according to both diary/diary by recall data and according to returned medication. Capsules taken per day, duration of treatment in days and reasons for stopping treatment will also be summarised by treatment arm and overall.

Compliance to diary completion will be summarised by treatment arm in

Table 9, including the number and frequency of patients returning their trial diary, proportion of diary completed, duration of diary completion, reasons for diary completion ending and number and frequency completing diary by recall.

4.4.2 Retention

The number and proportion of 12-week notes reviews completed, as well as the number of primary and secondary consultations recorded in the notes reviews will be summarised in **Table 12**. **Table 13** will summarise the length of retention in the study, measured as time from baseline to end of study, and also the withdrawal rate determined by number and proportion of patients providing complete useable endpoint data at 28 days and 12 weeks.

4.4.3 Effectiveness of blinding

The treatment allocation guessed by participants will be summarised as the number and frequency in each arm guessing each allocation in **Feasibility endpoint** information
Table 8. This table will also summarise the number and frequency of patients in each arm and overall guessing their allocation correctly, and the reasons for their choice.

4.5 Secondary endpoints

4.5.1 AECOPD treatment prescribing and use

Antibiotic prescribing and use will be summarised in

Table 10, by treatment arm and overall. This table will include the number of patients prescribed antibiotics at the initial GP consultation, the intended use of those antibiotics (immediate, delayed or as rescue medication) and the number of patients who took or were prescribed any antibiotics within 1 day and within 28 days of entering study.

Oral corticosteroid (OCS) prescribing and use will be summarised in **Table 11**, by treatment arm and overall. This table will include the number of patients prescribed antibiotics at the initial GP consultation, the intended use of those antibiotics (immediate, delayed or as rescue medication) and the number of patients who took or were prescribed any antibiotics within 1 day and within 28 days of entering study.

4.5.2 Distribution of patient reported outcome measure scores

Distribution of EXACT-PRO and CAT scores will be summarised for each treatment arm by day of completion in

Figure 2 and

Figure 3 respectively.

4.6 Safety reporting

All safety tables will use the ITT population split by treatment arm.

4.6.1 Adverse events

A summary of all adverse events (AEs) reported will be presented in **Table 14**. This table will show the total number of AEs, the number of patients that experienced at least one AE, the median number of AEs per patient and a summary of all AEs broken down by system organ class (SOC) term, preferred term and by AEs of special interest.

The worst CTCAE toxicity grade for each patient will be summarised in **Table 15** as well as the number of patients experiencing a severe (CTCAE grade 3 or above) adverse event using the safety population.

Table 16 summarises the number of patients that experienced at least one AE graded 3 or above and a summary of grade 3 or above AEs by system organ class (SOC), preferred term and by AEs of special interest.

4.6.2 Serious adverse events

Serious toxicity includes serious adverse events (SAEs), serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs). In this section the term “serious adverse events (SAEs)” encompasses SAEs, SARs, SUSARs.

Table 17 will present the total number of SAEs, the number of patients that experienced at least one SAE and the median number of SAEs per patient (for patients experiencing at least one SAE) by treatment arm. The PI assessment, the number of SAEs by CTCAE grade and the reason for their seriousness will also be presented for all SAEs by treatment arm.

The number of patients with at least one SAE will be summarised by SOC and preferred term for each treatment arm in **Table 18**. **Table 19** will present SAE summaries by SOC and preferred term for SAEs graded 3 and above only.

In addition, all SAEs (excluding maintenance phase) will be listed in **Table 20**.

5 Example tables, listings and figures

Tables:

Figures:

5.1 Disposition of study population

Figure 1 - CONSORT diagram

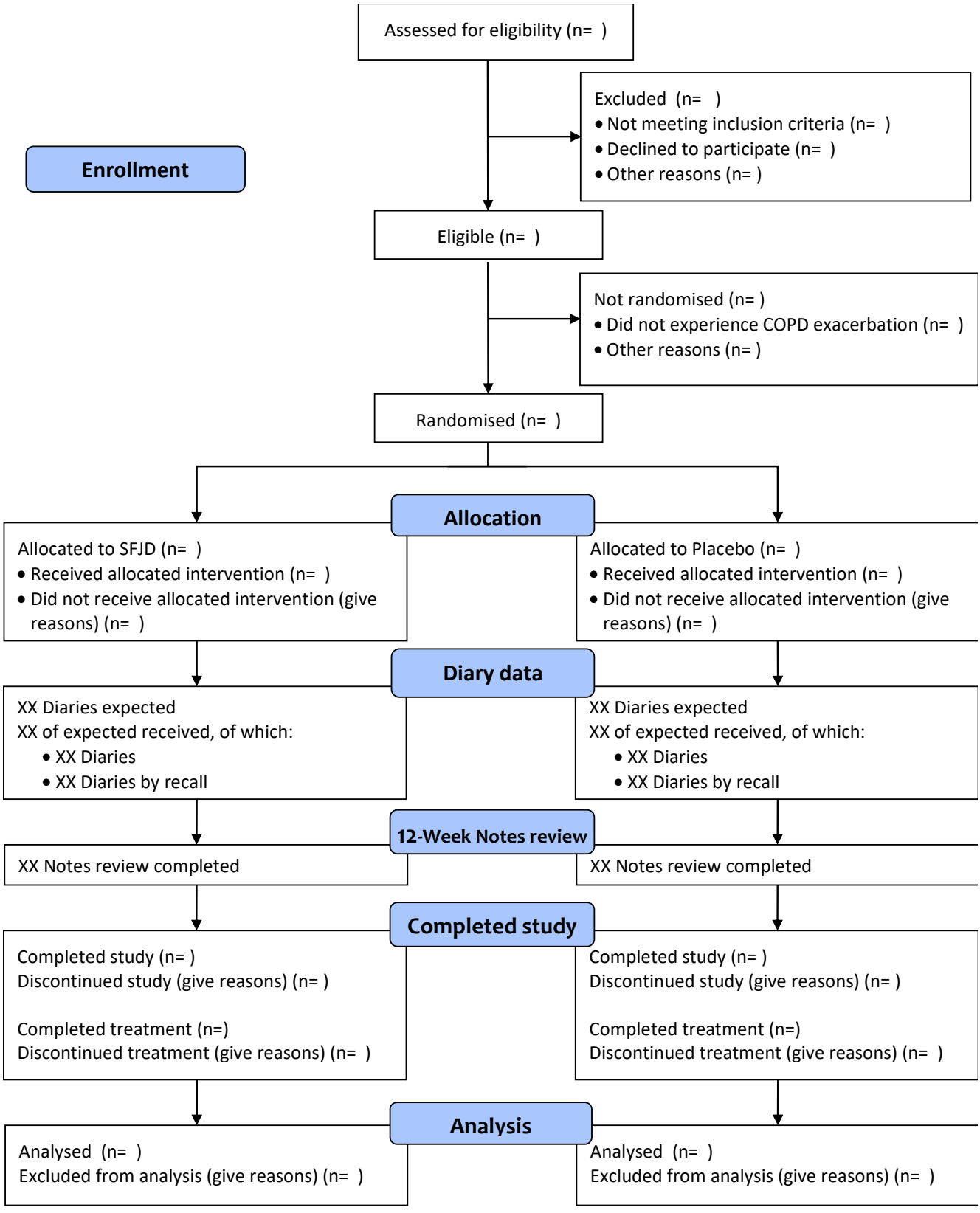


Table 1 Summary of populations

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Included in ITT population[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Excluded from ITT population[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 1[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…			

[1] These percentages are calculated using the number of patients in each group as the denominator
[2]These percentages are calculated using the number of patients who were excluded from the ITT population as the denominator

Table 2 Screening and recruitment information

Site no.	Site Name	PI Name	Activation Date	Total Screened	Total Randomised	Screen Failures	% Failure	Date first patient registered	Date most recent patient registered
Total									

Table 3 Recruitment information reported per site

Characteristic	Site								All sites (n=xx)
	Chawton Park (n=xx)	Highcliffe (n=xx)	Liphook & Liss (n=xx)	Oaks (n=xx)	Swanage (n=xx)	Three Chequers (n=xx)	Wareham (n=xx)	Westlands (n=xx)	
Patients on the COPD register presenting with AECOPD[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Patients on the COPD register presenting with AECOPD who are eligible and ineligible[2]									
Eligible	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ineligible	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reasons for ineligibility[3]									
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Eligible patients recruited[4]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Recruitment rate per 1000 registered COPD	xx	xx	xx	xx	xx	xx	xx	xx	xx

patients per month open[5]									

[1]These percentages are calculated using the number of patients on the COPD register at each site as the denominator.
[2]These percentages are calculated using the number of patients on the COPD register presenting with AECOPD at each site as the denominator.
[3]These percentages are calculated using the number of ineligible patients at each site as the denominator.
[4]These percentages are calculated using the number of eligible patients at each site as the denominator.
[5]Recruitment rate per 1000 registered COPD patients per month open calculated as 1000 x no. of participants recruited by site/no of registered COPD patients at site/no. of months site open.

5.2 Protocol Deviations

Table 4 Major protocol violations

Violation	Patient/site affected (if applicable)	Treatment arm (if applicable)	Comments	Actions
Xxxx	xxxx	xxxx	xxxx	xxxx

5.3 Baseline and Demographic Characteristics

Table 5 Demographic and subject characteristic information

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Age in years[1,3]			
n	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Sex – n (%)[1]			
Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Prefer not to say	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ethnicity – n (%)[1]			
White	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Black or Black British	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mixed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Asian or Asian British	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Chinese or other ethnic group	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Prefer not to answer	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Employment – n (%)[1]			
Employed (full or part-time, including self-employment)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Unable to work due to long-term illness / disability	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Retired from paid work	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Unemployed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
In full-time education	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not working for other reasons	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Smoking history – n (%)[1]			
Never	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Past	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Current	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cigarettes smoked per day[4]			
n	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[5]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Years smoked for[4]			
n	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[5]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other smoker(s) in household – n (%)[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

SD = standard deviation, IQR = inter-quartile range (quartile 1 to quartile 3)

[1]These percentages are calculated using the number of patients in each group with subject characteristics data available.

[2]These percentages are calculated using the number of patients in each group.

[3]Age data is as recorded on subject characteristics CRF

[4]These percentages are calculated using the number of patients in each group who are current or past smokers with relevant data available.

[5]These percentages are calculated using the number of patients in each group who are current or past smokers.

Table 6 Baseline clinical information

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Days experiencing COPD exacerbation[1]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
AECOPD Symptoms			
Increased sputum purulence – n (%)[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Increased sputum volume – n (%)[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Increased breathlessness – n (%)[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Heart rate (beats/min) [1]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Temperature (°C) [1]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Oxygen saturation level (%) [1]			

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Bronko test sputum colour [1]			
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Baseline CAT Score [1]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Baseline EXACT-PRO Score[1,3]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

SD = standard deviation, IQR = inter-quartile range (quartile 1 to quartile 3)

[1]These percentages are calculated using the number of patients in each group with subject characteristics data available.

[2]These percentages are calculated using the number of patients in each group.

[3]NOTE: If treatment is started on day 1 then baseline EXACT-PRO questionnaire will usually be completed after start of treatment.

Table 7 Relevant medical history

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
No. of patients with a relevant medical history condition or event[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Relevant medical history or event[1]			
Chronic kidney disease (stage 3 or lower)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Chronic heart failure	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cardiovascular disease	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hypertension	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Asthma	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Diabetes Mellitus	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Immunosuppression	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Relevant treatments[1]			
Anti-platelet medication	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Anti-diabetic medication	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Diuretics	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] These statistics or percentages are calculated using the number of patients in each group

5.4 Feasibility endpoint information

Table 8 Treatment information

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Compliance with medication (%)[1,2]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Compliance with medication according to returned medication (%)[1,4]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Compliance with medication according to Participant Diary (%)[1,5]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Compliance with medication according to Diary by Recall (%)[1,6]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Capsules taken per day according to Participant Diary[1,7]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Capsules taken per day according to Diary by Recall[1]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Difference in capsules taken per day according to Diary and Diary by Recall[1]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Duration of treatment according to returned medication (days)[1,8]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Duration of treatment according to Participant Diary (days)[1,9]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Duration of treatment according to Diary by Recall (days)[1]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reported side effects to trial medication in participant diary – n (%)[1]			
Week 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week 4			
Reasons for stopping treatment – n (%)[1]			
Completed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Intolerable side effects	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Symptoms resolved	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Symptoms did not resolve	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Treatment allocation guessed – n (%)[1]			
Active (SFJD)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Placebo	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Unsure	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Correct treatment allocation guessed – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reasons for believing allocation was SFJD – n (%)[10]			
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[11]			
Reasons for believing allocation was placebo – n (%)[10]			
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[11]			
Reasons for being unsure of allocation – n (%)[10]			
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[11]			

[1] These statistics or percentages are calculated using the number of patients in each group with treatment data available.
[2] Compliance with medication is calculated in order of preference using the methods below based on either returned medication; if not available then from Participant Diary; and finally, if both are not available then from Diary by Recall.
[3] These statistics or percentages are calculated using the number of patients in each group.
[4] Compliance with medication according to returned medication is calculated as (168 - number of capsules returned)/168.
[5] Compliance with medication according to Participant Diary: Calculated as sum of all capsules taken morning, midday and evening between day 1 and day 21 according to Trial Medication section of diary/168.
[6] Compliance with medication according to Diary by Recall: Calculated as no. of days trial medication taken for, multiplied by no. of capsules taken per day according to Diary by Recall/168.
[7] Capsules taken per day according to Participant Diary is calculated as total no. of capsules taken according to Participant Diary/no. of expected entries (3 per day) between first and last entry on which trial medication was >0, divided by 3
[8] Duration of treatment according to returned medication is calculated assuming full compliance of 12 capsules per day, as (168 – no. of returned capsules)/12.
[9] Duration of treatment according to Participant Diary is calculated as no. of expected medication entries between the first and last entries which are non-zero and non-missing, divided by 3.
[10] These percentages are calculated using the number of patients who guessed that allocation and provided a reason for doing so.
[11] These percentages are calculated using the number of patients who guessed that allocation.

Table 9 Diary completion

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Trial diary returned – n (%)[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Proportion of trial diary completed – n (%)[1]			
Complete Diaries (2 days confirmed symptom resolution)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Complete Diaries (7 days confirmed symptom resolution)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Incomplete Diaries with useable antibiotic use data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Incomplete Diaries with other useable endpoint data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Incomplete Diaries with unusable endpoint data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No Diary returned	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of days on which complete diary data was entered[1,2]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Duration of diary completion (days)[1]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Reasons for diary completion ending – n (%)[3]			
AECOPD ended and diary had been completed for at least 14 days	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
AECOPD ongoing but diary had been completed for all 28 days	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Did not wish to continue[4]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason did not wish to continue 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason did not wish to continue 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Diary by recall completed – n (%)[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
First day of symptom resolution (FDSR)[5]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
FDSR available according to Participant Diary – n (%)[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
FDSR according to Participant Diary[6]			
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
FDSR available according to Diary by Recall – n (%)[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
FDSR according to Diary by Recall			
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Unable to recall FDSR by Diary by Recall	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Better on day 7	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Better on day 14	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Better on day 21	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Difference between FDSR as recorded in Participant Diary vs Diary by Recall[7]			

N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Length of AECOPD (days)[8]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] These statistics or percentages are calculated using the number of patients in each group

[2] A day is considered to have complete diary data entered if the following diary sections, as applicable, have data entered; trial medication, antibiotics taken, steroids taken, symptom resolution, EXACT-PRO, CAT.

[3] These statistics or percentages are calculated using the number of patients in each group with reason for ending diary completion available.

[4] These statistics or percentages are calculated using the number of patients in each group with 'did not wish to continue' as reason for ending diary completion.

[5] If the Symptom Resolution section of the Participant Diary has a final entry of "No" (indicating that the patient has no AECOPD symptoms), then the first consecutive "No" entry will be used for the first day of symptom resolution. Otherwise, if the Symptom Resolution section of the Participant Diary has a final entry of "Yes" and the Diary By Recall has a resolution date after the date of last entry, then the diary by recall will be used.

[6] If the Symptom Resolution section of the Participant Diary has a final entry of "No" then the first consecutive "No" entry will be used for the first day of symptom resolution.

[7] Calculated as FDSR according to Participant Diary – FDSR according to Diary by Recall.

[8] Calculated as date of first day of symptom resolution – date of baseline visit + no. of days experiencing AECOPD recorded at baseline.

Table 10 Antibiotic use

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Number of patients prescribed antibiotics at initial GP consultation – n (%)[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Name of antibiotic prescribed at initial GP consultation – n (%)[3]			
e.g. Amoxycillin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Clarithromycin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Doxycycline	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(Other)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Intended use of prescribed antibiotics – n (%)[3]			
Immediate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Delayed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Rescue	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of patients taking antibiotics within 1 day of entering study[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Name of antibiotic taken within 1 day of entering study[4]			
e.g. Amoxycillin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Clarithromycin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Doxycycline	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(Other)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of patients prescribed antibiotics within 28 days of entering study[1]			

Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Name of antibiotics prescribed within 28 days of entering study[5,7]			
e.g. Amoxycillin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Clarithromycin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Doxycycline	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(Other)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of patients taking antibiotics within 28 days of entering study[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Name of antibiotics taken within 28 days of entering study[6,7]			
e.g. Amoxycillin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Clarithromycin	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Doxycycline	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(Other)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1]These percentages are calculated using the number of patients in each group with antibiotic use data available
[2]These percentages are calculated using the number of patients in each group
[3]These percentages are calculated using the number of patients in each group prescribed an antibiotic at initial GP consultation
[4]These percentages are calculated using the number of patients in each group who began taking an antibiotic within 1 day of entering study
[5]These percentages are calculated using the number of patients in each group who were prescribed an antibiotic within 28 days of entering study
[6]These percentages are calculated using the number of patients in each group who began taking an antibiotic within 28 days of entering study.
[7]NOTE: may add up to more than total n if some patients have taken multiple antibiotics within 28 days.

Table 11 Oral Corticosteroids (OCS) use

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
On maintenance OCS dose – n (%)[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Increased OCS dose prescribed at GP consultation, if on maintenance OCS – n (%)[3]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
OCS prescribed, if not on maintenance OCS – n (%)[4]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
OCS taken within 1 day of entering study – n (%)[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Type of OCS taken within 1 day of entering study – n (%)[1]			
e.g. Prednisolone	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Source of OCS taken within 1 day of entering study – n (%)[1]			
e.g. GP prescription	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Rescue pack	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…			
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
OCS taken within 28 days of entering study[1]			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1]These percentages are calculated using the number of patients in each group with OCS use data available
[2]These percentages are calculated using the number of patients in each group
[3]These percentages are calculated using the number of patients in each group with OCS use data available who are receiving maintenance OCS.
[4]These percentages are calculated using the number of patients in each group with OCS use data available who are not receiving maintenance OCS.

Table 12 Summary of 12-week Notes Review

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
No of participants with 12-week notes review completed – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No of participants with at least one primary care consultation within notes review period – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No of primary care consultations recorded within notes review period – n (%)[2]			
Nurse			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
GP			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
No of participants with at least one secondary care visit or admission within notes review period – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No of secondary care visits or admissions recorded within notes review period – n (%)[2]			
Outpatient visit			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Inpatient admission			
N	xx	xx	xx

Mean (SD) Median (IQR) Range	xx.x (xx.x) xx.x (xx.x to xx.x) xx.x to xx.x	xx.x (xx.x) xx.x (xx.x to xx.x) xx.x to xx.x	xx.x (xx.x) xx.x (xx.x to xx.x) xx.x to xx.x
Reason for secondary care visit/admission – n (%)[3]			
As recorded on discharge form	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…..	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

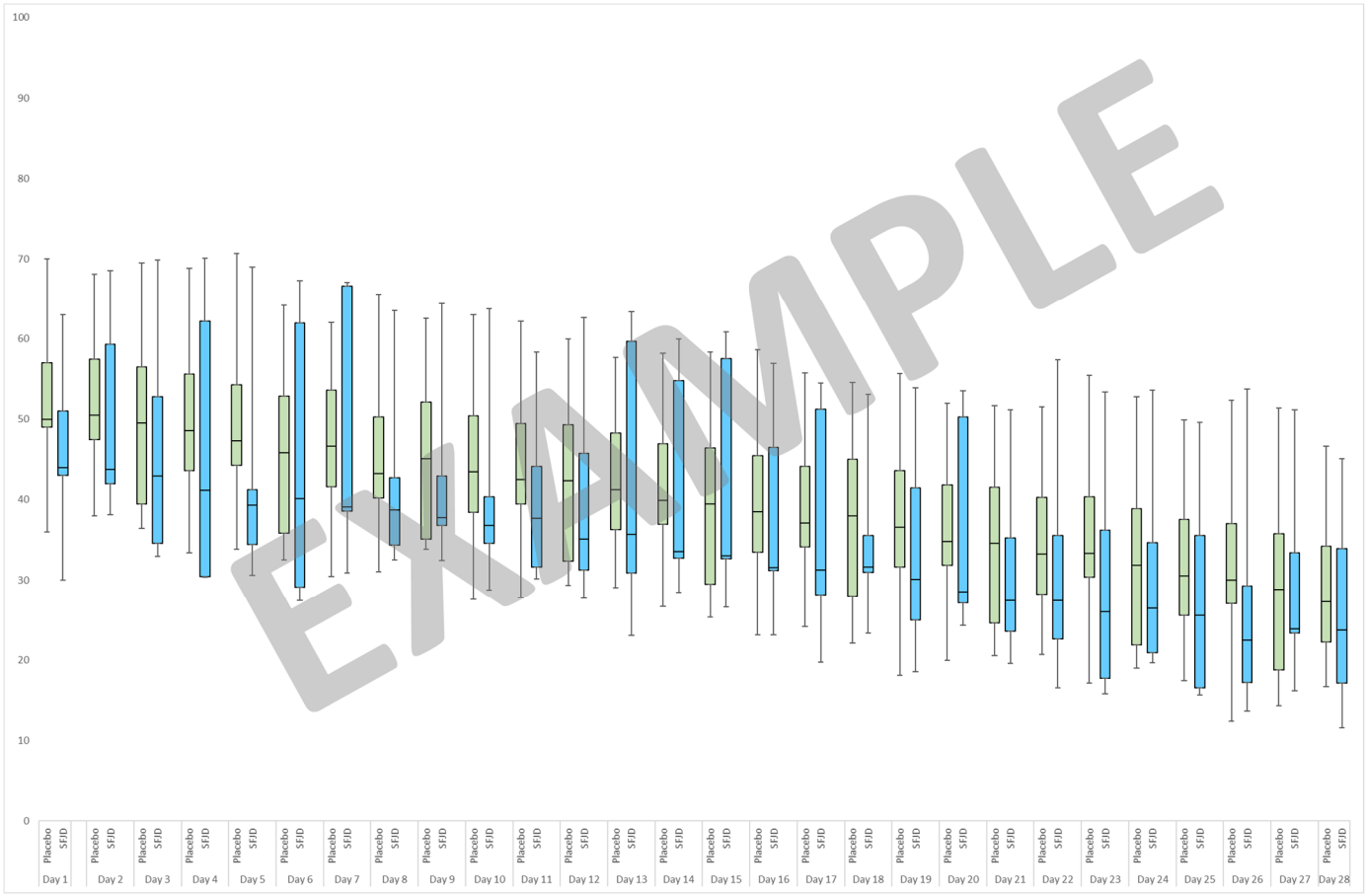
SD = standard deviation, IQR = inter-quartile range (quartile 1 to quartile 3)

[1]These percentages are calculated using the number of patients in each group

[2]These percentages are calculated using the number of patients in each group with 12-week notes review data available

[3]These percentages are calculated using the number of patients in each group with at least one secondary care outpatient visit/inpatient admission

Figure 2 Exact-Pro Scores: Boxplots from baseline (day 1) to day 28, by treatment arm



Day:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
No of EXACT-PRO questionnaires returned – n (%)[1]	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

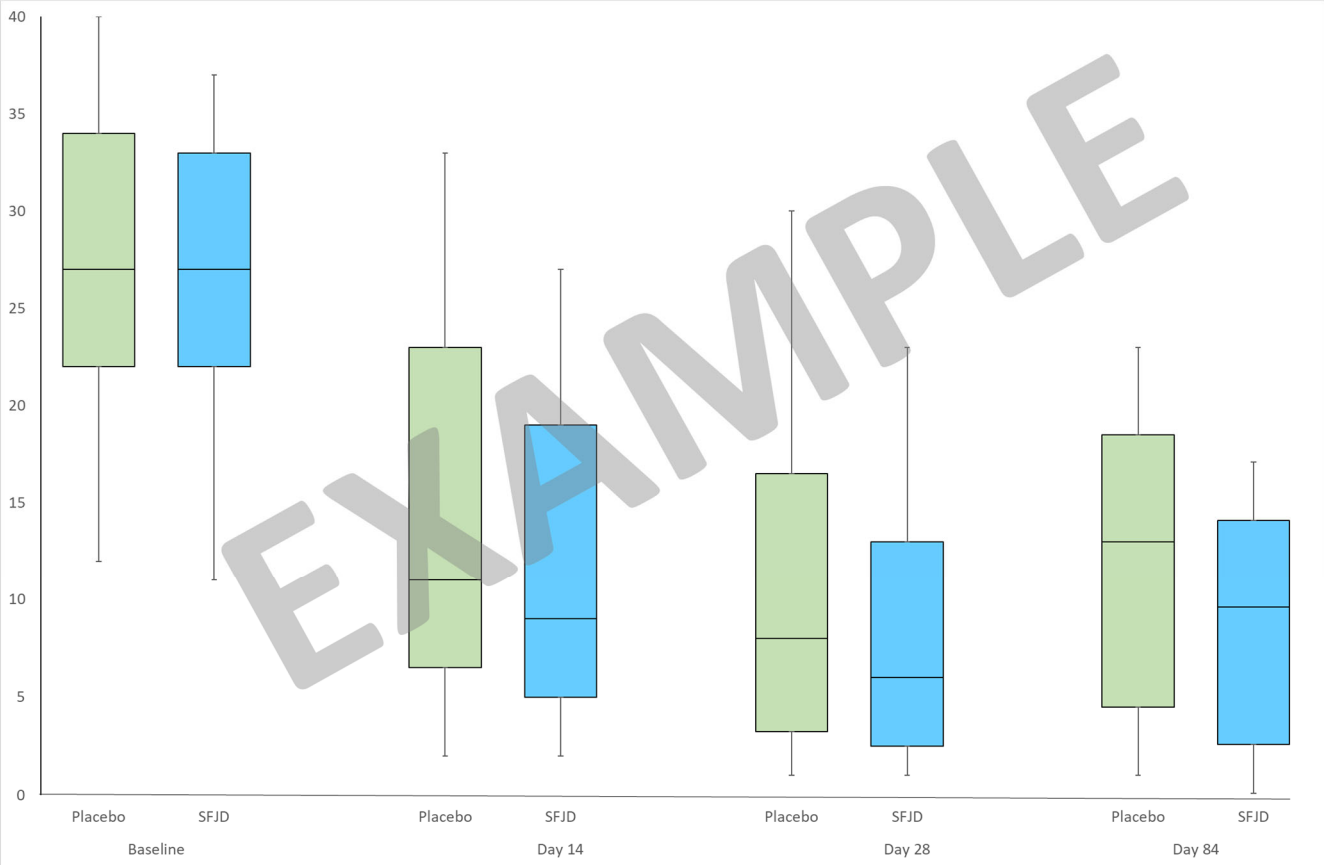
Day:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
No of fully completed EXACT-PRO questionnaires returned – n (%)[1]	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
EXACT-PRO Score (complete data)																												
SFJD group:																												
N	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Min	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q3	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Placebo group:																												
N	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Min	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q3	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
EXACT-PRO Score (incomplete data)																												
SFJD group:																												
N	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Min	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q3	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Placebo group:																												
N	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Min	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Day:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Q1	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q3	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

[1]These percentages are calculated using the number of patients in each group

NOTE: EXACT-PRO should be completed daily from Day 1 of treatment until **EITHER** the 14-day treatment is complete and resolution of their AECOPD symptoms have been maintained for 7 days; **OR** 28 days post-randomisation.

Figure 3 COPD Assessment Test (CAT) Scores: Boxplots from baseline (day 1) to day 84, by treatment arm



Day:	Baseline (Day 1)	Day 14	Day 28	Day 84
No of CAT questionnaires returned – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No of fully completed CAT questionnaires returned – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CAT Score				
SFJD group:				
N	xx	xx	xx	xx
Min	xx.x	xx.x	xx.x	xx.x
Q1	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Q3	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x
Placebo group:				
N	xx	xx	xx	xx

Day:	Baseline (Day 1)	Day 14	Day 28	Day 84
Min	xx.x	xx.x	xx.x	xx.x
Q1	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Q3	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x
CAT Score calculated using incomplete questionnaires				
SFJD group:				
N	xx	xx	xx	xx
Min	xx.x	xx.x	xx.x	xx.x
Q1	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Q3	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x
Placebo group:				
N	xx	xx	xx	xx
Min	xx.x	xx.x	xx.x	xx.x
Q1	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Q3	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x

[1]These percentages are calculated using the number of patients in each group

NOTE: EXACT-PRO should be completed daily from Day 1 of treatment until **EITHER** the 14 day treatment is complete and resolution of their AECOPD symptoms have been maintained for 7 days; **OR** 28 days post-randomisation.

Table 13 End of study information

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
No. end of study eCRF received – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for end of study – n (%)[2]			
Completed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Physician decision	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Withdrawal by subject	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lost to follow-Up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing from eCRF – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Time from baseline to end of study[2,3]			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Missing from eCRF – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No of patients providing complete useable endpoint data at 28 days – n (%)[1,4]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No of patients providing complete useable endpoint data at 12 weeks – n (%)[1,5]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] These statistics or percentages are calculated using the number of patients in each group
[2] These statistics or percentages are calculated using the number of patients in each group with EOS data available
[3]Time from baseline to end of study is calculated as date of end of study from EOS eCRF – date of baseline visit + 1 day.
[4]Calculated as no of patients who have completed all of the following data points at 28 days, either by diary or diary by recall: trial medication, antibiotics taken, steroids taken, symptom resolution, EXACT-PRO, CAT Questionnaire.
[5]Calculated as no. of patients who have provided a complete CAT Questionnaire at 12 weeks. .

5.5 Safety Reporting

Table 14 Overall toxicity

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Total number of adverse events – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of patients that experienced at least one AE – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of AEs per patient (for patients with at least one AE) – median (range)[2]	xx (xx.x - xx.x)	xx (xx.x - xx.x)	xx (xx.x - xx.x)
Summary of AEs – n (%)[1]			
Classification group 1 name	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Classification group 2 name	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Classification group XX name	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1]Denominator is the number of patients in each group
[2]These statistics are calculated using the number of patients in each group experiencing at least one AE

Table 15 Overall toxicity by CTCAE Grade

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Adverse events – n (%)[1,2]			
CTCAE 4.0 Grade 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 4.0 Grade 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 4.0 Grade 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 4.0 Grade 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 4.0 Grade 5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients in each group
[2] The worst grade is used when more than one grade is available for a patient

Table 16 Overall Toxicity (Grade 3 or above)

Characteristic	**SFJD (n=xx)**	**Placebo (n=xx)**	**Total (n=xx)**
Number of patients that experienced at least one AE graded 3 or above – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Summary of AEs graded 3 or above – n (%)[1]			
Classification group 1 name	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Classification group 2 name	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Classification group XX name	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients in each group

Table 17 Summary of the SAEs reported

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Total number of SAE/SAR/SUSARs – n	xx	xx	xx
Number of patients experiencing at least one SAE/SAR/SUSAR – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of SAE/SAR/SUSAR per patient (for patients with at least one SAE/SAR/SUSAR) – median (range)[2]	xx (xx to xx)	xx (xx to xx)	xx (xx to xx)
Overall assessment – n (%)[3]			
SUSAR (Suspected Unexpected Serious Adverse Reaction)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAR (Serious Adverse Reaction)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAE (Serious Adverse Event)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE v4.0 grade – n (%)[3]			
1 – Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 – Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 – Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 – Life threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 – Death related to AE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Why was the event serious – n (%)[3]			
1 – Resulted in death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 – Life threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 – Required hospitalisation or prolongation of existing hospitalisation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 – Persistent or significant disability/incapacity	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 – Congenital anomaly/birth defect	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
6 – Other important medical event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1]Denominator is the number of patients in each group.
[2]These statistics are calculated using the number of patients in each group experiencing at least one SAE/SAR/SUSAR
[3]Denominator is the number of SAEs/SARs/SUSARs.

Table 18 Summary of the main symptom(s) reported on the SAE form

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Number of patients experiencing at least one SAE/SAR/SUSAR – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Blood and lymphatic system disorders - n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cardiac disorders	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastrointestinal disorders	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…etc…			
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients in each group.

Table 19 Summary of the main symptom(s) reported on the SAE form (Grade 3 or above)

Characteristic	SFJD (n=xx)	Placebo (n=xx)	Total (n=xx)
Number of patients that experienced at least one SAE graded 3 or above – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Summary of SAEs graded 3 or above – n (%)[1]			
Blood and lymphatic system disorders	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cardiac disorders	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastrointestinal disorders	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…etc…			

[1] Denominator is the number of patients in each group.

Table 20 List of all SAEs reported

Patient ID	Treatment Arm	CTCAE Term	SOC	Date Identified by Site	Date of Onset	Date of most recent treatment administration	Grade[1]	Serious[2]	Action taken[3]	Causality[4]	Expectedness[5]	Overall Assessment

[1] CTCAE v4.0 Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life-threatening, 5=Death related to AE, ?=Awaiting classification.
[2] Why was the event serious: 1=Resulted in death, 2=Life-threatening, 3=Required hospitalisation or prolongation of existing hospitalisation, 4=Persistent or significant disability/incapacity, 5=Congenital anomaly/birth defect, 6=Other Important medical event, ?=Awaiting classification.
[3] Action taken due to SAE: 0=None, 1=Dose reduction, 2=Treatment delayed, 3=Treatment reduced & delayed, 4=Treatment stopped, ?=Awaiting classification
[4] Investigator's Opinion - Causal relationship to SAE: 1 = Definitely, 2 = Probably, 3 = Possibly, 4 = Unlikely, 5 = Not related
[5] Investigator's Opinion – Expectedness:

6 References

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7 SAP revision history

Version number	Revision history	Author	Date
0.1	SAP created	Kerensa Thorne	12-May-22
0.2	Updated following review by LS	Kerensa Thorne	24-Jun-22
0.3	Updated following review by LS	Kerensa Thorne	06-Jul-22
0.4	Updated following review by TO and discussion at data review meeting; tables 11 (OCS use) and 12 (12 week notes review) added	Kerensa Thorne	02-Aug-22
0.5	Updated following review by MM and MW at SAP review meeting	Kerensa Thorne	12-Sep-22
0.6	Updated category definitions in 'proportion of diary completed'.	Kerensa Thorne	01-Nov-22
1.0	Clean version created for approval	Kerensa Thorne	09-Nov-22