Statistical Analysis Plan	
Study Code	D5241C00001
Edition Number	4.0
Date	28 November 2023

A Randomised, Double-blind, Placebo-controlled, Parallel Group, Multicentre, Phase 2a Study to Explore the Efficacy and Safety of Tezepelumab in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) (COURSE)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AZ	Astrazeneca
BD	Bronchodilator
BP	Blood pressure
BMI	Body Mass Index
CAT	COPD assessment tool
CFB	Change from baseline
CI	Confidence interval
CID	Clinically important deterioration
COPD	Chronic obstructive pulmonary disease
COPDCompEx	Composite exacerbation event in COPD
COVID-19	Coronavirus Disease 2019
CSP	Clinical study protocol
CSR	Clinical study report
CV	Coefficient of variation
DAE	Discontinuation of investigational product due to adverse event
DBL	Database lock
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DL	Direct likelihood

Abbreviation or special term	Explanation
DRMI	Drop-out reason-based multiple imputation
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
EOT	End of treatment
ePRO	Electronic patient reported outcome
E-RS: COPD	Evaluating respiratory symptoms in chronic obstructive pulmonary disease
EXA	COPD exacerbation visit
EXACT-PRO	Exacerbations of chronic pulmonary disease tool – Patient-reported outcome
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
FeNO	Fractional exhaled nitric oxide
FVC	Forced Vital Capacity
ICF	Informed consent form
ICS	Inhaled corticosteroids
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IP	Investigational product
IPD	Investigational product discontinuation
IWRS	Interactive web response system
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LLOQ	Lower limit of quantification
LSMEANS	Least squares means

Abbreviation or special term	Explanation
MAR	Missing at random
MCID	Minimum clinically important difference
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-effect model for repeated measures
NHP	Non-compliance handling plan
MNAR	Missing not at random
N	Sample size
nAB	Neutralizing antibodies
N/A	Not applicable
NBD	Negative binomial distribution
NC	Not calculable
NQ	Non-quantifiable
PD	Protocol deviations
PK	Pharmacokinetics
PN	Percent normal
PRO	Patient reported outcome
PT	Preferred term
Q1	First quartile
Q3	Third quartile
Q4W	Every four weeks
RNA	Ribonucleic acid
SAE	Serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation

Abbreviation or special term	Explanation
SGRQ	St. George's respiratory questionnaire
SI	System international (units)
SOC	System organ class
SpO_2	Oxygen saturation
TBL	Total bilirubin
TSLP	Thymic stromal lymphopoietin
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
UNS	Unscheduled visit
WHO DD	World Health Organization Drug Dictionary

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentation	08NOV2023	Clarify the subgroup analyses model for FEV1 and SGRQ	N/A	To help with reporting and interpretation
Data presentation	08NOV2023	1. Add exposure adjusted event rate for SAE tables 2. Remove by SOC for AE by causality and maximum intensity tables	NA	To be consistent with AZ safety guidance
Data presentation	08NOV2023	1. Add definition of COVID19 pandemic end date 2. Remove efficacy and safety analyses using data between 1st September 2020 and 10th March 2021 3. Add sensitivity analysis of primary outcome variable for post-pandemic period	N/A	To follow global definition of pandemic and provide more accurate evaluation of impact of pandemic
Data presentation	08NOV2023	Add text to clarify number of prior exacerbations is number of prior exacerbations at randomisation	N/A	To help with reporting and interpretation
Data presentation	27JUN2023	1. Add baseline smoking status and COPD characteristics to the subgroups in Section 3.1.7 2. Add subgroup analyses for change from baseline in pre-dose/pre-BD FEV1 and SGRQ in Section 4.2.5.5 and 4.2.5.6	N/A	To help with reporting and interpretation
Data presentation	10MAR2023	Sections 3.2.3.1 and 4.2.6: Deleted “Time from 1st to 2nd COPDCompEx”	N/A	To help with reporting and interpretation
Other	10MAR2023	Section 5: Updated the time of data cutoff from 3 months to 1 month	N/A	To help accelerate potential planning of Phase 3 study
Data presentation	10MAR2023	Sections 3.3.3 and Appendix 8: Updated list and definitions of AESIs	Yes	To align with CSP v7.0 and development program
Statistical analysis methods	10MAR2023	Section 3.3.2: Updated time at risk definition to only consider the time up to the first occurrence of an adverse event	N/A	To be consistent with development program
Statistical analysis methods	10MAR2023	Section 4.2.5.5: Specified that only those subjects who have at least one non-missing post-baseline value will be included in	N/A	To provide additional clarity

		longitudinal models		
Statistical analysis methods	10MAR2023	Section 4.2.5.5: Specified that subject will be used in the REPEATED statement	N/A	To provide additional clarity
Data presentation	10MAR2023	Section 4.2.7.1: Added that AESIs and Severe infections (as collected on the dedicated eCRF) will be listed	N/A	To provide clarity that serious infections (an AESI) and severe infections (no longer an AESI) will be summarised separately for completeness
Other	09DEC021	Updated Section 3.4.2 to add clarity for nAb collection Updated Section 4.2.8.2 to specify the statistics analysis or nAb	N/A	To help with reporting and interpretation
Other	05NOV2021	Added rules for visit window of PK in Section 4.2.8.1	N/A	To help with reporting and interpretation
Other	13OCT2021	Added Week 52 for the analysis of COPDCompEx	N/A	To help with reporting and interpretation
Data presentation	13OCT2021	Added analysis of biomarkers in Section 4.2.6.2	N/A	To help with reporting and interpretation
Data presentation	15SEP2021	Deleted “Study drug administered per protocol” information from Section 4.2.3	N/A	To help with reporting and interpretation
Statistical analysis method for the primary or secondary endpoints	31AUG2021	1. Added text in Section 4 to specify that DDFM=KR and OBSMARGIN for LSMEANS will be used in MMRM models 2. Added Two more categories for subgroup analysis as well as text to address the situation of unbalanced subgroup categories causing convergence issues	N/A	To help with reporting and interpretation
Other	13MAY2021	Section 1.1.4 Exploratory Objectives: added clarification ‘during treatment phase’ to the objective ‘to evaluate the effect of tezepelumab on sputum biomarkers, sputum cell counts and sputum microbiome, in subjects participating in sub-study, at baseline, end of treatment, and at the start of all exacerbations.’	Yes	To be consistent with CSP v5.0
Other	13MAY2021	Updated sample size to 338 in Sections 1.2 and added clarification to screening period. Added clarification on requirements of signing COVID-19 addendum to inform consent prior to Revised the sample size to “169” per treatment arm in Figure 1	Yes	To be consistent with CSP v5.0

Other	13MAY2021	Section 1.3: Revised into two sections, "Original Sample Size", and "Updated Sample Size"	Yes	To be consistent with CSP v5.0
Data presentation	28MAY2021	Section 3.1.5: Updated the visit window at Week 40 to "267" as well as added logic for the visit of the last visit whenever the upper limit of the visit window is exceeded	N/A	Typo and to accommodate data collection
Data Presentation	28MAY2021	Added the imputation rule for AE/CM partially/missing date in Appendix 8.5	N/A	To add clarity in the imputation rule
Other	8DEC2020	Updated the study details Section 1.1 by adding the objectives for EXACT-PRO	Yes	To be consistent with CSP v4.0
Other	8DEC2020	Updated the study design Section 1.2 and Number of subjects in Section 1.3 to adjust for COVID-19 impact	Yes	To be consistent with CSP v4.0
Other	8DEC2020	Updated the definition of PK analysis in Section 2.1.3	Yes	To be consistent with CSP v4.0
Data presentation	22JAN2021	Updated text to address COVID-19 impact in Section 2.2	N/A	To reflect the impact of COVID-19 in the summary of PDs
Data presentation	4APR2020	Updated the definition of baseline for FEV1 and added the definition of baseline EXACT-PRO in Section 3.1.2, Removed "physical examination"	Yes	To include readings prior to 1st dose for FEV1 and to clarify the baseline definition for EXACT-PRO, in accordance with CSP v3.0
Derivation of primary or secondary endpoints	8DEC2020	Added text to clarify the duration of COPD exacerbation as well as updated text for symptom documentation3.2.1.1	Yes	To be consistent with CSP v4.0
Derivation of primary or secondary endpoints	1. 30SEP2020 2. 22JAN2021	1.Added text to clarify the handling of logically skipped items in the SGRQ in Section 3.2.2.6. 2. Updated "domain scores" to "component scores"	N/A	1.To ensure that logically skipped items in the SGRQ are not set to missing. 2. To be in line with the latest questionnaire
Other	7APR2020	Added "decrease" in the definition of MCID in Section 3.2.2.7	Yes	To help with derivation and interpretation
Other	30SEP2020	Updated source variables to be used in the derivation of the exploratory endpoint COPDCompEx in Section 3.2.3.1.	N/A	Original symptom variables specified are not all available in the eDiary or not measured on the same scale. Wheeze has been removed & the remaining 5 variables to be taken from EXACT-PRO.

				Daily rescue medication to be sum of morning and evening records for consistency with recall period of EXACT-PRO symptom scores.
Other	2APR2020	Added the definition of EXACT-PRO endpoint in Section 3.2.3.5 and its analysis in Section 4.2.6	Yes	To be consistent with CSP v3.0
Data presentations	8DEC2020	Added text to clarify data collection on few biomarkers in Section 3.2.3.9	Yes	To be consistent with CSP v3.0
Other	22JAN2021	Updated Section 4.2.1 to: 1. Added text to specify the denominator for percentage calculations in disposition analysis; 2. Added the analysis of IWRS stratification factors; 3. Changed the analysis set to "FAS" for summary of recruitment by country and centre; 4. Updated the medical history paragraph; 5. Added the analysis of COVID19 related PDs	N/A	To be consistent with Teze standard and to address the impact of COVID19
Other	22JAN2021	Added text for potential biologics for COPD in Section 4.2.2 and rearranged the paragraphs	N/A	To be consistent with Teze standard and to reflect the planned analysis
Other	22JAN2021	Added "study drug administration according to protocol" in Section 4.2.3	N/A	To help with understanding and interpretation of the results
Statistical analysis method for the primary or secondary endpoints	22JAN2021	In Section 4.2.4.1 - 1. Deleted on-treatment estimand and redefined the primary and supplemental estimand; 2. Added text for graphical presentation of historic COPD exacerbation; 3. Updated the text for summary of exacerbations with alert triggered and investigator justified	Yes	To be consistent with Teze standard and the CSP
Statistical analysis method for the primary or secondary endpoints	22JAN2021	Added text to reflect analyses due to COVID-19 disruptions in Section 4.2.4.2	N/A	To address the impact of COVID-19

Statistical analysis method for the primary or secondary endpoints	26FEB2021	Added text to clarify the data used for secondary endpoint analysis in Section 4.2.5	N/A	To add more clarity in derivation and reporting of the results
Statistical analysis method for the primary or secondary endpoints	21JAN2021	Emphasized the summary statistics of the Kaplan-Meier results for the time to first exacerbation at Week 52 in Section 4.2.5.1	N/A	To add more clarity in reporting of the results
Other	26FEB2021	Added text to specify the analysis type and reporting of the results in Section 4.2.5.3	N/A	To add more clarity in derivation and reporting of the results
Statistical analysis method for the primary or secondary endpoints	26FEB2021	Deleted on-treatment estimand and rephrased the primary and supplemental analysis in Section 4.2.5.5	Yes	To be consistent with Teze standard and the CSP
Other	1.30SEP2020 2.22JAN2021	In Section 4.2.6 - 1. Added text for handling intercurrent events; 2. Clarified the maximum follow up time for COPDCompEx analysis as well as added the graphical reporting of COPDCompEx events, Changed “Week 52” to “Week 12” in the analysis of this endpoint 3. Added text to clarify the analysis of specific resource utilisation	N/A	1. To clarify the maximum follow up time derivation for this analysis 2.To clarify the analysis type
Other	22JAN2021	Removed “AESI” from overall summary of AEs and removed the analysis for AESI anaphylactic reaction in Section 4.2.7.1	N/A	To be consistent with AZ safety guidance
Other	26FEB2021	Removed “missing” category from shift tables of laboratory data (Section 4.2.7.2) and vital signs (Section 4.2.7.3) 2. Removed “Mean change from baseline over time will also be plotted by treatment group” in Section 4.2.7.2	N/A	To be consistent with AZ safety guidance
Other	22JAN2021	Updated ADA section per latest Teze	N/A	To be consistent with AZ

		safety guidance		safety guidance
Other	8DEC2020	Added text to clarify the impact of COVID-19 in Interim analyses Section 5	Yes	To be consistent with CSP v4.0
Other	7APR2020	Added reference for EXACT-PRO variable in Section 7	N/A	To help with derivation of this added endpoint
Statistical analysis method for the primary or secondary endpoints	26FEB2021	In Appendix 8.2, for primary endpoint – 1. Removed sensitivity analysis for on-treatment estimand; 2. Updated text for sensitivity analysis under supplemental estimand; For secondary endpoints – 1. Removed sensitivity analysis for supplemental and on-treatment estimands Updated the efficacy estimands table in Appendix 8.3	N/A	To help interpretation of efficacy results of this study
Statistical analysis method for the primary or secondary endpoints	8DEC2020	Added Appendix 8.4 to summarise the analyses impact of COVID-19 disruptions	Yes	To be consistent with CSP v4.0

*Pre-specified categories are: Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other

1. STUDY DETAILS

This is the statistical analysis plan (SAP) for study D5241C00001. The SAP describes the statistical analyses specified in the latest version of the clinical study protocol (CSP) in more detail; any changes to what is specified in the CSP will be described in Section 6.

1.1 Study objectives

1.1.1 Primary objective

Primary Objective	Outcome Measure
To evaluate the effect of tezepelumab as compared with placebo on Chronic Obstructive Pulmonary Disease (COPD) exacerbations in subjects with moderate to very severe COPD	**Primary endpoint**: Rate of moderate or severe COPD exacerbations **Primary outcome measure:** Moderate or severe COPD exacerbation rate ratio (tezepelumab vs placebo) **Supportive endpoint**: Rate of moderate (excluding exacerbations treated only with antibiotics) or severe COPD exacerbations **Supportive measure**: Moderate (excluding exacerbations treated only with antibiotics) or severe COPD exacerbation rate ratio (tezepelumab vs placebo)

1.1.2 Secondary objectives

Secondary Objectives	Outcome Measure

To evaluate the effect of tezepelumab compared with placebo on time to first moderate/severe exacerbation	**Outcome variables:** • Time to first moderate or severe COPD exacerbation • Proportion of subjects with ≥1 moderate or severe COPD exacerbation **Outcome Measures:** • Hazard Ratio (tezepelumab vs placebo) • Odds Ratio (tezepelumab vs placebo)
Secondary Objectives	**Outcome Measure**
To evaluate the effect of tezepelumab as compared with placebo on severe COPD exacerbations	**Secondary outcome variable:** Rate of severe COPD exacerbations **Outcome measure:** Rate ratio (tezepelumab vs placebo) **Supportive outcome variables:** • Time to first severe COPD exacerbation • Proportions of subjects experiencing a severe COPD exacerbation **Supportive outcome measures:** • Hazard ratio (tezepelumab vs placebo) • Odds ratio (tezepelumab vs placebo)

To evaluate the effect of tezepelumab as compared with placebo on pre-bronchodilator (BD) lung function	**Outcome variable**: Change from baseline in pre-BD forced expiratory volume in 1 second (FEV_1) at Week 52 **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52
To evaluate the effect of tezepelumab as compared with placebo on respiratory health status/health-related quality of life	**Outcome variables**: • Proportion of subjects achieving a minimum clinically important difference (MCID) of 4 units or more in SGRQ total score at Week 52 • Change from baseline in SGRQ at Week 52 • Change from baseline in COPD assessment tool (CAT) at Week 52 **Outcome Measures:** • Odds Ratio (tezepelumab vs placebo) • Mean difference in change from baseline (tezepelumab vs placebo) at Week 52
To evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab	PK: Serum trough concentration Immunogenicity: Incidence of anti-drug antibodies (ADA)

1.1.3 Safety objectives

Safety Objective:	Safety Variables:
To assess the safety and tolerability of tezepelumab as compared with placebo in subjects with moderate to very severe COPD	Adverse events/serious adverse events (AEs/SAEs) Vital signs Laboratory assessments Electrocardiograms (ECG)

1.1.4 Exploratory objectives

Exploratory Objectives:	Exploratory Variables:
To explore the effect of tezepelumab on COPD Composite Exacerbations (COPDCompEx) event	**Outcome variable:** • Time to COPDCompEx event • Rate of COPDCompEx events **Outcome Measure:** • Hazard Ratio (tezepelumab vs placebo • Rate ratio (tezepelumab vs placebo) over first 12 weeks as well as 52 weeks treatment period
To explore the effect of tezepelumab on time to a Clinically Important Deterioration (CID) event	**Outcome variable:** Time to CID event **Outcome Measure:** Hazard Ratio (tezepelumab vs placebo)
To explore the impact of tezepelumab on blood eosinophil and neutrophil levels	**Outcome variable:** Change from baseline in blood eosinophil and neutrophil levels **Outcome measure:** Change from baseline at Week 52

Exploratory Objectives:	**Exploratory Variables:**
To explore the effect of tezepelumab on post-BD lung function (FEV_1)	**Outcome variable:** Change from baseline in post-BD forced expiratory volume in 1 second (FEV_1) **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52
To evaluate the effect of tezepelumab on respiratory symptoms and on the frequency, duration, and severity of EXACT-PRO defined events	**Outcome variable:** • Change from baseline in Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (EXACT-PRO/E-RS^{TM}: COPD) • Rate of EXACT-PRO defined exacerbations **Outcome measure:** • Mean difference in change from baseline (tezepelumab vs placebo) at Week 52 • EXACT-PRO defined exacerbation rate ratio (tezepelumab vs placebo)
To evaluate tezepelumab's effect on COPD-related healthcare resource utilisation	**Outcome variable:** Rate of COPD-specific resource utilisation (e.g. unscheduled physician visits, unscheduled phone calls to physicians, use of other COPD medications) **Outcome measure:** Difference in rate of COPD-specific resource utilisation (tezepelumab vs placebo) over 52 weeks

Exploratory Objectives:	**Exploratory Variables:**
To assess the effect of tezepelumab on airway inflammation	**Outcome variable:** Fractional exhaled nitric oxide (FeNO) **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52
To assess the effect of tezepelumab on total serum immunoglobulins	**Outcome variable:** Total immunoglobulins (IgE, IgA, IgM, IgG) **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52
To assess the effect of tezepelumab on blood biomarkers	Serum and plasma biomarkers including markers of remodeling and inflammation
To evaluate the effect of tezepelumab on sputum biomarkers, sputum cell counts and sputum microbiome in subjects participating in sub-study, at baseline, end of treatment, and at the start of all exacerbations during the treatment phase	• Sputum biomarkers of inflammation and remodeling • Sputum cell counts and cell differentials from cytospins • Sputum microbiome
To explore the effect of tezepelumab on the blood and/or nasal epithelial cell and/or sputum cell transcriptome for pharmacodynamic (PD) markers of exposure or response to tezepelumab and pre-and post-dose predictive markers of clinical response	Transcriptomic biomarkers (may include but not limited to): RNA-Seq and RNA microarray profiling and microbiome profiling. Transcriptomics analysis may be carried out on blood cells, and/or nasal epithelial cells and/or sputum cells
To evaluate the effect of tezepelumab on nasal lining fluid biomarkers	Nasal biomarkers including but not limited to inflammation and remodeling
To evaluate the effect of tezepelumab on urine biomarkers	Urine biomarkers including but not limited to inflammation and remodeling

Exploratory Objectives:	Exploratory Variables:
To explore the relationships between pharmacogenomic Deoxyribonucleic acid (DNA) markers and response/exposure to tezepelumab	Optional AZ genomics blood sample. Pharmacogenomic biomarkers may include (but not limited to): SNP and epigenetic
To explore the PK of tezepelumab in respiratory tract fluid	Tezepelumab concentrations in nasal lining fluid and/or sputum

1.2 Study design

This is a Phase 2a, multicenter, randomised, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of tezepelumab 420 mg administered by subcutaneous (SC) injection every 4 weeks (Q4W) in subjects with moderate to very severe COPD receiving triple inhaled maintenance therapy (inhaled corticosteroids (ICS), long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA)), and having had ≥2 documented COPD exacerbations in the 12 months prior to Visit 1. Approximately 30% of subjects will have had at least 1 severe exacerbation (an exacerbation resulting in hospitalisation) within the 12 months prior to Visit 1. Approximately 40% of subjects will have had ≥3 exacerbations within the 12 months prior to Visit 1.

The study will consist of a screening period for approximately 6 weeks, a treatment period of 52 weeks and a post-treatment follow-up period of 12 weeks. Subjects will be randomised in a 1:1 ratio to either 420 mg of tezepelumab or matching placebo both administered Q4W SC. During the treatment period, investigational product (IP) will be administered from Day 1 until Week 48. No IP will be administered at Week 52. Subjects that complete the 52-week study visit will complete a 12 week off-treatment follow-up period for assessments. Subjects who discontinue IP during the study will be encouraged to undergo appropriate study visits/procedures for the full 52-week period.

The study will randomise approximately 338 subjects 1:1 to either tezepelumab or placebo, stratified by region, and number of prior exacerbations recorded at randomisation in IWRS. Approximately 20% of the subjects will be targeted to have ≥300 eosinophils/μL, approximately 40% of the subjects between ≥150 to <300 eosinophils/μL and a maximum of approximately 40% of the subjects with <150 eosinophils/μL at enrolment. When the target percentage of subjects for the prior exacerbations or eosinophil subgroup in a region or overall is reached, consideration will be given to closing the Interactive Web Response System (IWRS) randomisation for that subgroup [by region or overall]. Once a subgroup is closed, subjects in the screening period in the closed subgroup will not be allowed to be randomised and will be screen failed.

Induced sputum analyses will be performed in a subset of subjects and in a limited number of sites globally. The aim of the induced sputum subset analysis is to explore the mechanisms by which

tezepelumab might reduce COPD exacerbations. In these same selected subjects, analysis of nasal lining fluid and epithelial transcriptomics will also be performed.

Pre-visit assessment during COVID-19 pandemic

Subjects must be contacted by telephone for assessment of possible COVID-19 symptoms within 72 hours prior to every study visit (except remote visits), as specified in CSP, Appendix I.

Screening period (Enrolment and Run-in)

After the initial enrolment period and confirmation of the eligibility criteria at Visit 1, subjects will proceed to the run-in period at Visit 2 for approximately 5 weeks to allow adequate time for all the eligibility criteria to be evaluated, as specified in the CSP, Table 1.

The screening lung function assessments and ECG can only be done when there are no restrictions to medications and Visit 1 SARS-CoV-2 naso/oropharyngeal swab test result is available and negative. If the SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result will not be available on day of Visit 1, the screening lung function assessments and ECG must be postponed until next visit, the postponed Visit 1, after the SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result is confirmed negative.

At a minimum, the following assessments/activities must be performed at Visit 1: obtain informed consent, temperature measurement, enrolment of subject in IWRS and SARS-CoV-2 naso/oropharyngeal swab test. The remaining Visit 1 assessments can be postponed together with the screening lung function assessments and ECG. At the postponed Visit 1, the spirometry equipment will allow pre-BD, post-BD spirometry, FeNO and ECG (combined Visit 1 and Visit 2) to be performed.

Visit 2 should be scheduled, if the Visit 2 post-BD spirometry and FeNO were not done at the postponed Visit 1. Preferably, Visit 2 should be scheduled no later than 1 week after Visit 1 but the enrolment can be extended to accommodate additional waiting time required to obtain Visit 1 SARS-CoV-2 naso/oropharyngeal swab test result.

The 35 day run-in can be extended by:

- 4 days for all subjects (maximum run-in duration is then 39 days) or
- 14 days (including 4 days for all subjects) for subjects with exacerbation or respiratory infection (excluding pneumonia) during screening (maximum run-in duration is then 49 days)
- waiting time required to obtain Visit 1 SARS-CoV-2 naso/oropharyngeal swab test result
- 28 days for patients receiving COVID-19 vaccine during screening
- 28 days for waiting time required to receive central lab kits

The 35 day run-in can be shortened by:

- 4 days for all subjects (run-in duration is then 31 days)

During the enrolment period, subjects must undergo all assessments as detailed in Table 1 of the CSP. At the end of the run-in period, subjects must continue to have a CAT score ≥15, 70% compliance with the maintenance therapy and acceptable compliance with the eDiary in order to be randomised to treatment. If a subject does not meet all inclusion criteria or meets any exclusion criteria as per section 5.1 and section 5.2 of the CSP, the subject will be screen failed.

Randomisation, Treatment and Follow-up

After randomisation subjects will be treated at monthly intervals with the last IP at Week 48. The end-of-treatment (EOT) visit (Week 52) will occur 4 weeks after last IP at Week 48. Follow-up visits will occur at Week 58 and Week 64 to allow for determination of immunogenicity and evaluation of safety. Subjects will be maintained on their currently prescribed maintenance therapies from enrolment throughout the run-in and treatment period. During the treatment period, subjects must undergo all assessments as detailed in Table 2 of the CSP.

During the COVID-19 pandemic, a phone call visit can replace an on-site visit and on-site IP administration can be replaced with home/alternative location IP administration. Subject must sign the COVID-19 addendum to informed consent prior to starting the alternative options of on- site IP administration. If obtaining signed addendum is not feasible, subject can follow alternative options after verbal consenting as specified in CSP, Appendix I.

The subject will enter the COPD exacerbation visit (EXA) and complete the assessments according to Table 2 of the CSP if he/she experiences a COPD exacerbation during the treatment period, if deemed necessary by Investigator.

The subject can also return to the site to complete an unscheduled visit (UNS) for the following reasons but not limited to, missed assessment(s) at last scheduled visit, safety follow up, issues with equipment, or other reasons that the site deems necessary. The UNS visit should not be the reason for a COPD exacerbation as there is an EXA visit for this reason. In addition to the assessments listed in CSP Table 2, other assessments may be performed at the Principal Investigator (PI)’s discretion.

Discontinuation of study treatment

Subjects are free to discontinue IP or withdraw from the study at any time without prejudice to further treatment. Discontinuing study treatment is not the same as study withdrawal. In the case of early study withdrawal, the EOT visit should be completed immediately. Subjects who do not wish to have any follow-up contacts as detailed below, will be withdrawn from the study. Procedures to follow for study withdrawal are detailed in Section 7.3 of CSP. All withdrawn subjects must return the eDiary device at the EOT visit (and at IP discontinuation (IPD) visit for subjects choosing option 3 below). If the subject

decides to withdraw consent, then the reason for this must be recorded separately in the electronic case report form (eCRF).

All subjects who prematurely discontinue IP should return to the site and complete the procedures described in Section 7.1.1 of CSP for the premature IPD visit at 4 weeks (+/-5 days) post last IP administration. Subjects who discontinue treatment should be encouraged to return for all regularly scheduled visits for safety and efficacy assessments.

At the IPD visit the subject will be given three options as to how they will be followed as follows:

1. The subject should be encouraged to return for all regular clinic visits and perform all scheduled assessments (excluding IP administration) until the EOT visit at Week 52 (+/-5 days).

2. The subject will be offered follow-up on a monthly basis via telephone calls while continuing eDiary completion (no further procedures will be performed) until the subject completes the EOT visit at Week 52 (+/-5 days). In addition to the Patient Reported Outcome (PRO) assessments that are performed at home, the subject may also complete the other clinic specified PRO assessments (as defined in Table 2 of CSP) at home as well.

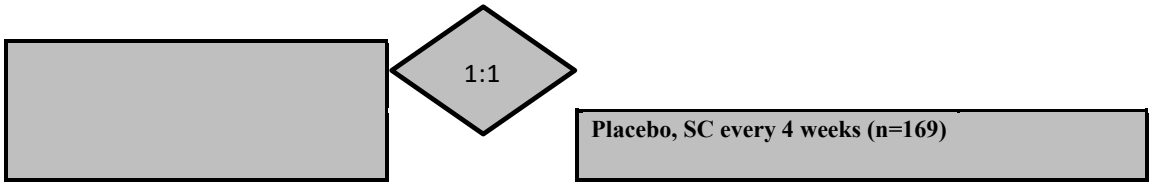
3. If the subject cannot or does not wish to comply with any of the options above, (or any component of them such as only telephone-based visits without completion of the eDiary), the Investigator will only contact the subject at 52 weeks post-randomisation. No other study assessments will be performed prior to this contact.

More details regarding procedures for discontinuation of study treatment are given in Section 7.1.1 of CSP.

The general study design is summarised in Figure 1.

Figure 1 - Study Flow Chart

<table>
<tr><th>V1</th><th>V2</th><th>R/V3</th><th>V4-V15</th><th>EOT/V16</th><th>V17, V18</th></tr>
<tr><td>Week
-6</td><td>Week
-5</td><td>Week
0</td><td>Week
4-48</td><td>Week
52</td><td>Week
58, 64</td></tr>
<tr><td>Enrolment</td><td>Screening/Run-in</td><td colspan="3">Treatment Phase</td><td>Follow-up</td></tr>
<tr><td colspan="2">Enrolment, Screening/Run-in</td><td></td><td colspan="3">Tezepelumab 420 mg, SC every 4 weeks (n=169)</td></tr>
</table>



1.3 Number of subjects

Original Sample Size

Approximately 282 subjects will be randomised to either tezepelumab or placebo (1:1) globally from over 80 sites. The subjects will be stratified by region [North America (USA, Canada), Europe (France, Germany, Netherlands, Spain, United Kingdom, Israel, Denmark,), Asia (South Korea)], and prior number of exacerbations (2 vs ≥3). Since the primary analysis of the primary endpoint will include all available data, including after treatment discontinuation, no need is envisaged to adjust the number of subjects planned to be randomised to obtain a number of evaluable subjects.

For the primary endpoint of reduction in COPD exacerbation rate, 141 subjects per treatment arm (282 total) will be randomised to achieve 80% power of detecting a 30% reduction in tezepelumab versus placebo over a fixed time period of 52 weeks. This calculation has assumed a one-sided 5% alpha level test, an annual placebo rate of 1.6 events/subject/52 weeks, a negative binomial shape parameter of 0.6, and 10% uniform drop out.

In the absence of the interim analysis for futility, this design would provide 81.2% power, and only 136 subjects per treatment arm would be required for 80% power.

This power statement accounts for the power loss associated with the futility interim analysis that will occur when 182 subjects have been randomised. In simulated results, 1.2% of simulated trials were stopped early for futility but would have been successful at the final analysis of the primary endpoint had they been allowed to continue. Therefore, the overall power for this trial accounting for the interim analysis is 80%. Note that as a result of the pause in recruitment due to COVID-19, the futility analysis is now planned to occur when approximately 30% of follow-up data is available but the expected power loss will be comparable under these conditions.

The primary endpoint will also be tested using a one-sided 2.5% alpha level test, but the sample size has not been determined based on providing power for this test.

Updated Sample Size

The sample size has been reassessed due to the potential for reduced exacerbation rates due to limited person-to-person contact and exposure to respiratory infections during the COVID-19 pandemic. Assuming the same treatment effect (0.7) and dispersion parameter (0.6) as originally assumed, a sample size of 169 subjects per treatment arm (338 overall) will maintain the study power if the placebo exacerbation rate is as low as 1.2 exacerbations/subject-year.

2. ANALYSIS SETS

2.1 Definition of analysis sets

All subjects analysis set:

This analysis set comprises all enrolled subjects who signed the informed consent form (ICF), including screening failures, and will be used for the reporting of disposition.

Randomised subjects analysis set:

This analysis set comprises all subjects randomised to study treatment, irrespective of whether IP was subsequently taken, and will also be used for the reporting of disposition.

2.1.1 Efficacy analysis Set

Full analysis set (FAS)

This analysis set comprises all subjects randomised to study treatment who received at least one dose of IP, irrespective of their protocol adherence, and continued participation in the study.

Efficacy analyses will be performed using all subjects in the FAS. Subjects will be analysed according to their randomised treatment (including in the case of any discrepancies between randomised and actual treatment at one or more visits).

The FAS specifies which subjects are included in efficacy analyses. Details of which data are included in efficacy analyses for these subjects are given in the respective sections, notably in Section 2.1.5, Section 3.1.4, and Section 3.1.5.

For consistency with efficacy analyses, demographics and baseline characteristics will be summarised using this analysis set as well.

Certain types of exploratory efficacy data are planned to be captured in a subset of participating subjects who have given an additional consent to participate in such a sub-study. Where this is the case, the analysis will use the subset of subjects in the FAS for which any data of the relevant type are available. No formal sub-study analysis sets will be explicitly defined for this purpose.

2.1.2 Safety analysis set

Safety analysis set

This analysis set comprises all subjects who received at least one dose of IP.

Safety analyses will be performed using all subjects in the safety analysis set. Subjects will be analysed according to their actual treatment in the case of any discrepancies between randomised and actual treatment. Specifically, a subject randomised to placebo who has on one or more occasion actually received active (tezepelumab) treatment will be assigned to the tezepelumab group, regardless of the randomised treatment assignment. A subject who has on no occasion actually received any active (tezepelumab) treatment will be assigned to the placebo group, regardless of the randomised treatment assignment.

Safety data will also be listed separately and discussed in the clinical study report (CSR) for any subject who received a treatment at one or more visits which was not the randomised treatment.

Summaries of anti-drug antibodies (ADA) will also be based on the safety analysis set, using the same approach to handle treatment dispensing errors.

2.1.3 Other analysis set

PK analysis set

This analysis set comprises all subjects who received at least one dose of tezepelumab and have at least one detectable serum concentration post first dose that is not affected by factors such as protocol deviations (e.g. disallowed medication or incorrect study medication received).

All PK summaries will be based on this analysis set.

2.1.4 Handling of other issues which may impact analysis sets

If it is found that any subject has been randomised on more than one occasion (contrary to the protocol) under different subject numbers, either at the same site or at different sites, then the first subject occurrence will be included in the relevant analysis sets defined above, and only data associated with that first subject occurrence will be used in analysis. Data associated with the second (and any subsequent) occurrences of the same subject will be listed and discussed in the CSR but will not be included in the summaries. All data associated with duplicate randomisations will be reviewed, and decisions regarding the analysis and reporting of these data will be documented, prior to unblinding.

The above analysis set definitions assume the integrity of data captured from all participating sites in the trial. If it is deemed necessary to exclude subjects from analysis sets due to suspected fraud/other serious non-compliance at a particular site, or to perform sensitivity analyses with subjects from such a site removed for the same reason, this will be documented in this SAP (amended if necessary) where this is possible prior to the primary Data Base Lock (DBL). Otherwise, it will be fully described in the CSR. The SAP will not be updated for this after DBL.

2.1.5 Definition of on-treatment

Efficacy analyses

The main efficacy analyses will use all available data for a subject who qualifies for the FAS, including off-treatment data up to Week 52 for subjects who discontinue IP early.

Some efficacy analyses will also be performed on subjects in the FAS which is restricted to on-treatment data. For this purpose, any efficacy assessment date which occurs between the date of randomisation and minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal) will be considered on-treatment. In particular, this allows a subject who completes treatment according to the protocol to have their Week 52 data included as on treatment, provided Week 52 is within the protocol visit window after the last dose of IP at Week 48.

Safety analyses

Safety analyses will be presented for subjects in the safety analysis set, which is described further in Section 2.1.2.

For this purpose, any adverse event start date, or any safety assessment date (e.g. laboratory, vital signs), which occurs between the date of first dose of IP and minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal) will be considered on-treatment. In particular, this allows inclusion of any safety-related information which may be reported at or generated from the IPD visit to be considered as on-treatment, provided the IPD visit is within the protocol visit window after premature discontinuation of IP.

2.2 Violations and deviations

Important protocol deviations (PDs) will be listed and tabulated in the CSR for randomised subjects (i.e. not screening failures). These are defined as PDs which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a subject's rights, safety or well-being. Important PDs in this trial will be grouped under one of the following categories:

- Subjects who did not meet the inclusion criteria
- Subjects who met the exclusion criteria
- Subjects who developed discontinuation criteria for study product but were not withdrawn from study treatment
- Subjects who met the discontinuation criteria for overall study withdrawal but were not withdrawn from study

- Subjects with investigational product deviations (e.g. who received the wrong treatment or an incorrect dose)
- Subjects who received the excluded concomitant medications
- Subjects with deviations related to study procedures
- Subjects with other potential important deviations

All important PDs will be identified and documented by the study team prior to unblinding of the trial. As far as possible, the occurrence of important PDs will be monitored (blinded) during the trial, with the emphasis on their future prevention.

Important PDs will not be used to exclude any subject from any analysis set, nor to exclude any data from subjects included in an analysis set.

The study Non-compliance Handling Plan (NHP) outlines the management of PDs and includes the proposed categories of PDs in this trial. Any PDs which are not defined as important or COVID-19 related will not be reported and discussed in the CSR.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General definitions

3.1.1 Age calculation

Age will be derived from the date of informed consent - date of birth, rounded down to the nearest integer. For subjects in countries where date of birth is not recorded, the age as recorded in the eCRF will be used.

3.1.2 Definition of baseline

In general, the last non-missing measurement on or prior to the date of randomisation will serve as the baseline measurement for efficacy variables. If there is no value on or prior to the date of randomisation, then the baseline value will not be imputed, and will be set to missing.

In general, the last non-missing measurement prior to first dose of study treatment will serve as the baseline measurement for safety variables. If there is no value prior to first dose of study treatment, then the baseline value will not be imputed, and will be set to missing.

Where unscheduled/repeat assessments are relevant and exist for any subject at a particular visit specified below, they will also be considered in the baseline definitions, provided they remain prior to the date of randomisation (efficacy) or the date of first dose of study treatment (safety).

According to the anticipated scheduling in the protocol, the following specific rules for the various data captured are proposed:

For categorical baseline respiratory disease characteristics captured directly in the eCRF (e.g. captured as ‘yes’ or ‘no’), if ‘yes’ is indicated in any visit during enrolment (scheduled or unscheduled), ‘yes’ will be used.

For clinic visit spirometry variables, the latest measurement recorded prior to first dose of study drug will be used as baseline.

For daily assessments which are made in both morning and evening, the whole day is defined by the assessments in the evening and the following morning. The daily assessment will be considered missing if either evening or following morning is missing. However, some analyses may consider morning and evening separately.

For SGRQ, the value at the randomisation visit (Visit 3) will be used as baseline.

For CAT, the value at the randomisation visit (Visit 3) will be used as baseline. If the Visit 3 measurement is missing, the screening value (Visit 1) will be used as baseline instead.

For evaluating respiratory symptoms in chronic obstructive pulmonary disease (E-RS: COPD), data collected in the last 14 days prior to randomisation will be used to calculate the individual E-RS: COPD total and subscale baseline means. If more than 7 daily measures/scores (>50%) are missing, then baseline is set to missing.

For EXACT-PRO, the baseline total score will be the mean score for each subject over the 7 days prior to randomisation. A minimum of 4 days of data (>50%) is required for calculating the baseline total score. To allow for improvement or deterioration in disease state over the course of the trial, the baseline total score will be reset every 4 weeks in the absence of an EXACT-PRO defined event.

For rescue medication use and nights with awakenings due to COPD symptoms, baseline is defined as the mean from the last 14 days prior to the date of randomisation and will be derived from data collected on the evening of Study Day -14 to the morning of Study Day 1. The biweekly mean is calculated as the sum of all non-missing daily measures/scores over 14 sequential days, divided by the number of non-missing daily measures/scores. If more than 7 daily measures/scores (>50%) within the baseline period are missing, then baseline is set to missing.

For clinic visit FENO, the value at the randomisation visit (Visit 3) will be used as baseline. If the Visit 3 measurement is missing, the run-in value will be used as baseline instead.

For safety variables (vital signs, weight/Body Mass Index (BMI), haematology, clinical chemistry, urinalysis, 12-lead ECG), baseline will be defined as the latest non-missing assessment prior to first dose. If no time is recorded for an assessment, and the assessment takes place at Visit 3, this will be assumed to be a pre-dose assessment.

For laboratory biomarkers, the value at the randomisation visit (Visit 3) will be used as baseline. For those variables assessed at screening (including eosinophils and total immunoglobulin), if the Visit 3 measurement is missing, the screening value will be used as baseline instead. For those variables not assessed at screening, then baseline will be missing.

For sputum and nasal sub-study assessment, the value at the randomisation visit (Visit 3) will be used as baseline. If the Visit 3 measurement is missing or if the sample cannot be assessed, the subject will be excluded from the sub-study.

3.1.3 Absolute change from baseline

Absolute change from baseline is defined as *(post-baseline value – baseline value)*.

Percent change from baseline is computed as

100 x ((post-baseline value – baseline value) / baseline value) %.

If either the post-baseline value or the baseline value is missing, then the absolute change from baseline will also be missing. If baseline value is zero, then percent change from baseline will be set to missing.

Unless otherwise specified, “change from baseline” is assumed to be the absolute change from baseline.

3.1.4 Study periods

The following study periods are defined for analysis purposes:

- Screening/run-in period: starting on the date of the first study procedure and ending one day prior to randomisation (for randomised subjects) or on the date of the last study procedure (for screening failures). If any subject is re-screened, the latest available screening will be used for this purpose.
- Planned treatment period (on-treatment and off-treatment): starting on the date of randomisation (efficacy) / date of first dose of IP (safety) and ending on the date of the Week 52 visit or earlier study withdrawal date (for subjects not followed up until Week 52).
- On-treatment period: starting and ending on the start and end dates defined in Section 2.1.5 for efficacy and safety analyses.

- Post-treatment period: starting one day after the end date defined in Section 2.1.5 for efficacy and safety analyses and ending on the study completion or withdrawal date.

- On-study period (planned treatment and follow-up): starting on the date of randomisation (efficacy) / date of first dose of IP (safety) and ending on the study completion or withdrawal date.

3.1.5 Visit windows

All summaries and analyses, both efficacy and safety, which are presented by time point (e.g. "Week 52") will use a visit window to classify the data record, which is derived from the assessment date relative to the reference start date. This approach allows appropriate classification of visits which may have occurred significantly earlier or later than the protocol assessment schedule, as well as the use of data captured at visits which have no fixed timing (notably the IPD visit), and the handling of data captured at visits for which the database label is incorrect and unresolvable.

Nominal database visit numbers will not be used in any summary or analysis by visit.

For efficacy and safety variables, the reference start date is the date of randomisation, and relative day is therefore defined as *(Date of assessment – Date of randomisation) + 1*.

Any data collected at unscheduled or repeat visits will be listed. These data will be included in baseline definitions (see Section 3.1.2) and in any definitions of maximum value, minimum value or last value within the relevant study period.

Data collected at unscheduled or repeat visits will also be included in visit windows, and therefore may be included in summaries or analyses by visit, or used in any sensitivity analyses which involve imputation of data from subjects with non-missing values to subjects with missing values. In the case of a missing value at a scheduled visit, which is then followed by a non-missing value at an unscheduled or repeat assessment within the same visit window, the non-missing value at the unscheduled/repeat assessment will replace the missing value at the scheduled visit.

If a subject has more than one non-missing value within the same visit window, the following rules will apply:

- The non-missing value closest to the target day will be selected for analysis at that visit

- If two non-missing values are the same distance from the target day, the earlier of the two values will be selected for analysis at that visit

- If two non-missing values are recorded on the same day and have a different assessment time associated with both of them, the value with the earliest assessment time will be selected for analysis at that visit

- If two non-missing values are recorded on the same day and have no assessment time associated with at least one of them, or the same assessment time associated with both of them, the average of the two values will be selected for analysis at that visit

If a subject has no value within a particular visit window, then the subject will have a missing value at that visit in summaries and analysis.

The same visit window definitions below will be used regardless of whether the planned treatment period or the on-treatment period is used for analysis (see Section 3.1.4). Each data record in the planned treatment period will be first identified, and then further flagged according to whether it is on-treatment or off-treatment. This flag will be used to select all eligible records for subsequent visit windowing, according to whether the derived visits are to be used in a planned treatment period or an on-treatment period analysis. It should be noted that, if treatment was discontinued within a particular visit window, the rules above for handling multiple values within the same visit window could select a different record according to whether a planned treatment period analysis or an on-treatment period analysis is needed.

In planned treatment period analyses any off-treatment assessments measured at a follow-up visit, which occurred earlier than scheduled follow-up visits Week 58, or Week 64, will be considered in an earlier planned treatment period visit window, where applicable.

Visit windows have been constructed so that every observation collected can be allocated to a particular visit, including unscheduled assessments. No visit windows will be defined for screening visits.

The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day. The window for the final scheduled visit collection should extend to the actual assessment date for the visit or to the scheduled study day if the visit is not completed.

For each analysis parameter, the windowing will be based on the protocol-specified schedule of events as defined in Tables 1 and 2 of the protocol.

Table 1 summarises the visits windows corresponding to the full (mostly 4-weekly) protocol scheduling clinic visits.

Table 1 Visit windows

Time point	Target day	Visit Window
Baseline (Week 0)	1	See Section 3.1.2 for baseline definitions
Week 4	29	2-42
Week 8	57	43-70
Week 12	85	71-98
Week 16	113	99-126
Week 20	141	127-154
Week 24	169	155-182
Week 28	197	183-210
Week 32	225	211-238
Week 36	253	239-266
Week 40	281	267-294
Week 44	309	295-322
Week 48	337	323-350
Week 52	365	351-385
Follow-up Week 58	407	386-427
Follow-up Week 64	449	428-469

For the exacerbation-related analyses, no windows will be applied. For endpoints that present visit-based data, the variables will be summarised based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined visit windows will be based on the collection schedule listed in the protocol and variables will be windowed to the closest scheduled visit for that variable.

For pre-bronchodilator FEV_1 (L), the non-missing value with acceptable quality (acceptable or borderline quality grade) which is closest to the scheduled visit will be included in the analysis. For post-bronchodilator FEV_1(L), the highest value with acceptable quality from the same date as the pre-bronchodilator FEV_1(L) result will be used. Assessments with missing quality grade will be assumed to have acceptable quality.

For overall analyses not based on any particular study visit (e.g., maximum post-baseline value), all data will be listed and/or analysed, including any repeat or unscheduled visits, unless otherwise specified. For safety endpoints, all post-baseline results will be included in these overall analyses, up to and including the end of treatment Visit 16 (EOT) visit.

3.1.6 Prior and concomitant medication

Medications taken by any subject at any time during the study will be coded using the Anatomical Therapeutic Chemical (ATC) classification system within the World Health Organisation (WHO) Drug Dictionary.

Medications will be categorised for analysis according to their onset and end dates as follows:

- Prior medications:
  - end date ≤ date of first dose of IP
- Concomitant medications during on-treatment period:
  - end date > date of first dose of IP and start date ≤ minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal), or
  - end date ongoing and start date ≤ minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal)
- Concomitant medications during post-treatment period (for subjects still being followed up then):
  - start date > date of last dose of IP + 33 days

Background COPD medication (i.e., triple therapy) will be classified as a 'COPD medication at baseline' if it started on or prior to randomisation and ongoing after randomisation.

If the medication record has a completely missing onset date, the subject will be assumed to have been on the medication on the date of the first study procedure. If the medication record has a partially missing onset date (month/year or year only) which is the same as that for the end of IP treatment, it will be assumed to have started on-treatment. If the medication record has a partially missing onset date (month/year or year only) which is the same as that for the start of IP treatment, it will be assumed to have started before treatment.

If the medication record has a completely missing end date, the subject will be assumed to have been on the medication on the date of study completion or withdrawal. If the medication record has a partially missing end date (month/year or year only) which is the same as that for start of IP treatment, it will be assumed to have ended on-treatment. If the medication record has a partially missing end date (month/year or year only) which is the same as that for end of IP treatment, it will be assumed to have ended post-treatment.

3.1.7 Definition of subgroups

The following subgroups are defined for the purpose of primary efficacy subgroup analysis and for secondary efficacy subgroup analysis (SGRQ and pre-BD FEV_1 only):

- Screening blood eosinophils group: <150/µL, ≥150/µL
- Baseline blood eosinophils group: <150/µL, ≥150 to <300/µL, ≥300/µL
- Baseline clinic visit FeNO group 1: <25ppb, ≥25ppb
- Baseline clinic visit FeNO group 2: <25ppb, ≥25 to <50ppb, ≥50ppb
- Age category at study entry: ≥40 to <65 years, ≥65 to <80 years
- Gender: Male, Female
- Race: White, Black or African American, Asian, Other
- Baseline Body Mass Index (BMI): <25 kg/m^2, ≥25 to 30 kg/m^2, ≥30 kg/m^2
- Chronic bronchitis at baseline (presence or absence of chronic bronchitis as recorded in RESHISTE module of the eCRF)
- Emphysema at baseline (presence or absence of emphysema as recorded in RESHISTE module of the eCRF)
- COPD characteristics at baseline (No emphysema or chronic bronchitis, Only emphysema, Only chronic bronchitis, Emphysema and chronic bronchitis as recorded in RESHISTE module of the eCRF)
- Prior severe exacerbation at randomization as recorded in eCRF: Yes, No
- Prior exacerbation counts recorded at randomisation as recorded in IWRS: 2, ≥3
- Baseline smoking status: Current, Former
- Baseline smoking status: ≥baseline median number of pack years, <baseline median number of pack years

3.2 Derivation of efficacy variables

3.2.1 Primary endpoint

3.2.1.1 The annual rate of COPD exacerbations

The annual rate of COPD exacerbations over 52 weeks will be used as the primary efficacy variable. A COPD exacerbation will be defined as a change in the subject's usual COPD symptoms that is beyond normal day-to-day variation, is acute in onset, lasts 2 or more days (or less if the worsening is so rapid and profound that the treating physician judges that intensification of treatment cannot be delayed), and may warrant a change in regular medication and leads to any of the following:

- Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids
- Use of antibiotics for at least 3 days
- An inpatient hospitalisation due to COPD (defined as an inpatient admission ≥24 hours in the hospital, in an observation area, the emergency department or other equivalent healthcare facility depending on the country and healthcare system)
- Results in death

All protocol-defined COPD exacerbations must fulfil the criteria above and be supported either by an eDiary alert, with duration recorded in the eCRF or by an investigator justification. Symptoms will be recorded in the eCRF only if an eDiary alert was not generated. All COPD exacerbations recorded in the eCRF, including investigator justified exacerbations, will be included in analyses provided they are not within 7 days of a prior exacerbation as defined below.

A COPD exacerbation will be considered **severe** if it results in at least 1 of the following:

- Hospitalisation due to the COPD exacerbation
- The subject being admitted for ≥ 24 hours to an observation area, the emergency department, or other equivalent healthcare facility (depending on the country and healthcare system) for the COPD exacerbation
- Death related to COPD or COPD exacerbation

A COPD exacerbation that does not meet the requirements to be classified as severe will be considered **moderate** if it results in at least one of the following:

- Use of systemic corticosteroids and/or antibiotics for at least 3 days
- A single depot injectable dose of corticosteroids, which will be considered equivalent to at least 3-day course of systemic corticosteroids

In order to calculate the number of exacerbations experienced by a subject during the treatment period, the following rule will be applied:

The start of an exacerbation is defined as the start date of systemic corticosteroids or antibiotic treatment or hospital admission, whichever occurs earlier, and the end date is defined as the last day of systemic corticosteroids or antibiotic treatment or hospital discharge, whichever occurs later.

A single depot injectable dose of corticosteroids will be considered equivalent to at least 3-day course of systemic corticosteroids. The corresponding stop date for this treatment will consequently be determined as the date of administration plus 2 days. If multiple treatments are prescribed for the same exacerbation, the earliest start date and the latest stop date will be used. For a severe COPD exacerbation with no documented corticosteroid or antibiotics treatment, hospitalization admission/discharge dates, or emergency visit date will be used as start/stop dates.

In the event of partial or missing start or stop dates recorded in the eCRF for systemic corticosteroids, antibiotic treatment, or hospital admission, the partial or missing start or stop dates will be imputed based on the overall exacerbation start and end dates as specified above.

Two or more exacerbations with the same start date and end date will be counted as one exacerbation for the purposes of calculating the number and duration of exacerbations for a subject. In such cases, severity will be the maximum severity of the events. In the case that one or more exacerbations are recorded as starting or ending during another exacerbation, these will be counted as one exacerbation, using the earliest exacerbation start date and the latest exacerbation stop date to calculate duration.

Additional systemic corticosteroid treatments, emergency room visits requiring use of systemic corticosteroids, or inpatient hospitalisation due to COPD occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted as a new exacerbation it must be preceded by at least 7 days in which none of the exacerbation criteria are fulfilled, i.e. if the end date of the first exacerbation and the start date of the second exacerbation are $\leq$7 days apart, then these will be counted as one exacerbation.

The maximum follow-up time for exacerbations for a subject is approximately 52 weeks; defined under the primary estimand as the time from randomisation to the date of Visit 16 (EOT), regardless of whether subjects remain on randomised treatment. For a subject lost to follow-up or prematurely withdrawing from the study prior to Visit 16 (EOT), this will be defined as the time from randomisation to the time point after which an exacerbation could not be assessed. For subjects who discontinue study treatment and remain in the study after the IPD visit, exacerbations will be counted from the time of randomisation up to and including the date of Visit 16 (EOT). Exacerbations that start after Visit 16 (EOT) will not be included in the efficacy assessments but will be listed. If a subject misses Visit 16 (EOT), then any exacerbations that start after the scheduled Visit 16 (EOT) date will be excluded from efficacy assessments. If an exacerbation is ongoing at Visit 16 (EOT), the exacerbation will be counted in the calculation of annual exacerbation rate, however the maximum follow-up time will be truncated at

the date of Visit 16 (EOT), as will the duration of exacerbation. For the subjects who died during the treatment period the exacerbation data collected up to the date of death will be included in the statistical analysis.

The number of days that the subject experiences an exacerbation during the follow-up time, including the subsequent 7 days (when a further exacerbation would not be considered a separate event (and if within the follow-up time)) will be subtracted from the maximum follow-up time to give the maximum time at risk of exacerbation.

In the primary analysis, the number of COPD exacerbations experienced by a subject during their follow-up time will be used as response variable.

The on-treatment annual exacerbation rate will be calculated similarly, as sensitivity analysis, using exacerbations occurring during the on-treatment period as defined in Section 2.1.5. The same formula for annual exacerbation rate will be used for all the estimands in Section 4.2.4.1, and for the corresponding sensitivity analysis in Appendix 8.2.

3.2.1.2 Additional supportive endpoint to primary

The annual rate of moderate or severe COPD exacerbations, excluding those moderate exacerbations treated only with antibiotics, will be used as a supportive endpoint for the primary endpoint. It will be derived similarly to the primary endpoint in Section 3.2.1.1, and includes all severe COPD exacerbations and moderate COPD exacerbations treated by oral corticosteroids (OCS) with or without antibiotics.

3.2.2 Secondary endpoints

3.2.2.1 Time to first COPD exacerbation

Time from randomisation to the first moderate or severe COPD exacerbation up to Week 52 will be a secondary efficacy variable, and is calculated as follows:

Start date of first COPD exacerbation – Date of randomisation + 1

An exacerbation event will be defined in the same way as outlined in Section 3.2.1.1. The time to first COPD exacerbation for subjects who complete Visit 16 (EOT) and do not experience a COPD exacerbation will be censored at Visit 16 date. For subjects who are lost to follow-up, prematurely withdraw from the study or discontinue the study treatment and remain in the study, the time to first COPD exacerbation will be censored at the end of the maximum follow-up time, as described in Section 3.2.1.1.

3.2.2.2 Proportion of subjects exacerbation free at Week 52

The proportion of subjects exacerbation free at Week 52 will be a secondary efficacy variable.

A moderate or severe exacerbation event will be defined in the same way as outlined in Section 3.2.1.1. In the statistical analysis, a binary variable taking on the value 1 if a subject has not experienced any moderate or severe exacerbations from randomisation to Visit 16 (EOT) and 0 otherwise, will be used as the response variable. The response variable will be set to 0 for subjects who withdraw early without completing Visit 16 (EOT).

3.2.2.3 Annual rate of severe COPD exacerbations

The annual rate of severe COPD exacerbations over 52 weeks will be a secondary efficacy variable. If the cause of any death is related to COPD or a COPD exacerbation, the event will also be included.

In the analysis, the number of severe COPD exacerbations will be used as response variable. The annual rate of severe COPD exacerbations will be derived similarly to primary endpoint in Section 3.2.1.1 and will be used for the production of summary statistics.

3.2.2.4 Time to first severe COPD exacerbation

A severe exacerbation event will be defined in the same way as outlined in Section 3.2.1.1.

Time from randomisation to first severe COPD exacerbation through Visit 16 (EOT) will be derived using the same approach as in Section.3.2.2.1. The time to first severe COPD exacerbation for subjects who complete Visit 16 (EOT) and do not experience a severe COPD exacerbation will be censored at Visit 16 date. For subjects lost to follow-up, prematurely withdrawing from the study, or discontinue the study treatment and remain in the study, the time to first severe COPD exacerbation will be censored at the end of the maximum follow-up time, as described in Section 3.2.1.1.

3.2.2.5 Change from baseline in pre-dose/pre-BD FEV_1 (L) at Week 52

Pre-dose/pre-BD FEV_1 (L) will be determined by spirometry at the clinic visit. The change in FEV1 (L) from baseline to each of the post-randomisation visits (post Visit 3) up to and including the Week 52 visit (Visit 16) will be assessed with change from baseline at Week 52 used as the secondary efficacy variable.

Change from baseline is obtained as an absolute difference between Week 52 measure and the baseline value as defined in Section 3.1.2 and Section 3.1.3. Changes from baseline at other post-baseline time points will be calculated similarly.

3.2.2.6 St. George's Respiratory Questionnaire (SGRQ)

The change from baseline in SGRQ total score up to Week 52 will be another secondary endpoint.

The SGRQ is a 50-item PRO instrument developed to measure the health status of subjects with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into two parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and three component scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the component scores range from 0 to 100, with higher scores indicative of greater impairment. SGRQ will be completed using an electronic subject diary (eDiary) as specified in Table 2 of the CSP.

The symptoms component score will be set to missing if there are >2 missing items; activity component score will be set to missing if there are >4 missing items; impacts component score will be set to missing if there are >6 missing items; and total score will be set to missing if one of the 3 component scores is missing.

To avoid incorrectly setting component and/or total scores to missing when items are logically skipped, the following items should **not** be considered as missing if logically skipped in the context of the subject's prior responses:

Question 6 (Length of worst attack of chest trouble):

If no severe or very bad, unpleasant attacks of chest trouble are reported in Q5, the length of the worst attack (Q6) will be logically skipped and should be imputed as zero, with the weight for Q6 remaining in the denominator.

Question 8 (Wheeze worse in the morning):

If the frequency of wheezing attacks is reported as 'None' in Q4, Q8 ('Wheezing worse in the morning') will be logically skipped and should be imputed as zero, with the weight for Q8 remaining in the denominator.

Question 14 (Medication does not help very much, Embarrassed using medication in public, Having side effects from medication, Medication interferes with life a lot):

If a subject is not taking any relevant medication, Q14 will be logically skipped. Therefore, if **all 4** responses are missing, all should be imputed as zero and the denominator for the component / total score(s) unchanged.

Potential health status treatment benefits of tezepelumab will be evaluated by comparing the change from baseline at Week 52 in SGRQ total score. A 4-point threshold will be used to define the response. If SGRQ total score at Week 52 has a ≥4-point decrease from baseline, it is defined as "improvement";

if it has a ≥4-point increase, it is defined as "worsening". If the SGRQ total score change at Week 52 is less than 4-points, it will be defined as "no change". Missing SGRQ total score change at Week 52 will be considered as "not evaluable". For the responder analysis of SGRQ, a responder will be defined as an individual who had "improvement" at Week 52 (i.e., ≥4-point decrease in SGRQ total score at Week 52). Subjects who had SGRQ total score change defined as "no change" or "worsening" will be considered as non-responders. If SGRQ total score change at Week 52 is not evaluable due to missing data, then the subject will also be treated as non-responder.

3.2.2.7 Proportion of subjects achieving a decrease of ≥4-points in SGRQ total score at Week 52 (MCID)

Based on empirical data and interviews with subjects, a decrease of ≥4-points in SGRQ total score at Week 52 is associated with a MCID and all the subjects meeting this criterion (as a decrease from baseline) are classified as responders, as defined in Section 3.2.2.6. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009).

In the statistical analysis, a binary variable taking on the value 1 if a subject has experienced a MCID at Visit 16 (EOT) and 0 otherwise, will be used as the response variable.

3.2.2.8 COPD Assessment Test (CAT)

The CAT is an 8-item PRO developed to measure the impact of COPD on health status (Jones et al 2009). The instrument uses semantic differential six-point response scales, which are defined by contrasting adjectives to capture the impact of COPD. Content includes items related to cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep and energy. A CAT total score is the sum of item responses. Scores range from 0-40 with higher scores indicative of greater COPD impact on health status. A score cannot be calculated if >2 responses are missing; when one or two items are missing, their scores can be set to the average of the non-missing item scores.

The CAT will be measured at visits in accordance to Table 1 and Table 2 of the CSP.

3.2.2.9 Additional supportive endpoints to secondary

To evaluate the effect of tezepelumab as compared to placebo on severe COPD exacerbations, proportion of subjects with ≥1 severe COPD exacerbations will be used as supportive variable to the secondary efficacy variable.

A severe exacerbation event will be defined in the same way as outlined in Section 3.2.1.1. In the statistical analysis, a binary variable taking on the value 1 if a subject has experienced one or more severe exacerbations during the 52-week double blind treatment period and 0 otherwise, will be used as response variable.

3.2.3 Exploratory endpoints

3.2.3.1 Composite Exacerbations (COPDCompEx) event

A composite endpoint for exacerbations (moderate or severe) in COPD (COPDCompEx) will be derived and analysed. COPDCompEx combines exacerbations with events defined from subject daily diaries. The definitions for both types of exacerbation are as follows:

- Exacerbations: episodes leading to one or more of the following: hospitalisation, emergency room visit, treatment with systematic corticosteroids, or treatment with antibiotics.
- Diary events: defined by meeting threshold and/or slope criteria for the following diary variables: breathlessness, cough, sputum, sleep, chest tightness, and rescue medication use. Breathlessness, cough, sputum, sleep, and chest tightness scores will be taken from the EXACT-PRO eDiary (recorded daily, in the evening) using variables EXACT07, EXACT02, EXACT03, EXACT13 and EXACT06 respectively, all of which are measured on a scale of 1-5. Rescue medication use will be calculated as described in Section 3.2.3.6 EXCEPT that daily use will be the sum of the morning and evening use **from the same day** (so that daily use is from evening to evening, to be consistent with the EXACT-PRO diary score recall period).

Threshold criteria:

- An increase of at least 2 puffs from baseline in rescue medication use (during 24h),

and

- An increase from baseline of at least 1 unit or maximum scores in all of the following symptom scores (during 24h): breathlessness, cough, sputum, sleep, and chest tightness.

Slope criteria:

- Need to meet the threshold criterion for at least one variable (either rescue medication use, breathlessness, cough, sputum, sleep or chest tightness) for two consecutive days (for the same symptom variable),

and

- Need to have the slope of a regression fit in the preceding 5 days to meet the following for all 6 variables:
  - Rescue medication slope $\geq$ 0.3 doses/day
  - Breathlessness slope $\geq$ 0.1 units/day
  - Cough slope $\geq$ 0.1 units/day
  - Sputum slope $\geq$ 0.1 units/day
  - Sleep slope $\geq$ 0.1 units/day

– Chest Tightness slope ≥ 0.1 units/day

In all of the above cases, the regression slope is the point estimate of the slope obtained from a linear regression of the values of each of the 6 variables separately against day number, with no other variables included in the regression model.

The following table shows how the timing for the 5-day requirement for the regression slopes fits with the 2 consecutive day requirement, where "Day 0" here refers to the first of the 2 consecutive days (shaded) to be used each time the rolling 2 consecutive day assessment is made:

Table 2 Timing for assessment of COPDCompEx slope criterion

	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1
Threshold					x	x
Slope	x	x	x	x	x	

A regression slope will be calculated provided there are at least 2 non-missing values in the required 5 days. Day 0 must be at least 1 day after the treatment start date to be able to estimate the slope.

Baseline is determined as the average of each variable using the 14 last days of the run-in period for each subject.

The start date of a COPDCompEx event is defined as the earliest of the exacerbation or diary events start dates which meets the definition. Exacerbation start date is as stated in Section 3.2.1.1. Diary event start date is defined as the earliest Day 0 (in notation from above table) from any series of rolling 2 consecutive days which first qualifies using either the threshold or slope criterion.

The end date of a COPDCompEx event is defined as the latest of the exacerbation or diary events start dates which meets the definition. Exacerbation end date is as stated in Section 3.2.1.1. Diary event end date is defined as the latest Day 1 (in notation from above table) from any series of rolling 2 consecutive days which last qualifies using either the threshold or slope criterion.

Similarly to the primary endpoint, if the end date of the first COPDCompEx event and the start date of the second COPDCompEx event are less than 7 days apart for any subject, then these will be counted as one COPDCompEx event.

The analysis of this endpoint will primarily be time to first COPDCompEx event defined similarly to the secondary endpoint in Section 3.2.2.1, namely

Start date of first COPDCompEx event - Date of randomisation + 1

If a subject presents either an exacerbation as described above, or any diary event meeting the threshold and slope criteria, COPDCompEx will be 1 (otherwise it will be 0). For those subjects with COPDCompEx=1 the date when the event (either exacerbation, or diary events) occurred will be also recorded. Subjects with COPDCompEx=0 will be considered as censored in that period. The date of censoring will follow the same rules as for time to first COPD exacerbation in Section 3.2.2.1.

In addition, the annual COPDCompEx rate, defined similarly to the primary endpoint in Section 3.2.1.1, in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model. The maximum follow-up time will be up to Week 12 (Visit 6) and Week 52 (Visit 16) with the assessment of the last COPDCompEx event status widened to also include additional consideration of the last assessment of various eDiary events used in the COPDCompEx definition. For subjects who prematurely withdraw from the study prior to Week 12 (Visit 6) or Week 52, the follow up time will be up to the date of the last assessment available.

3.2.3.2 Clinically Important Deterioration (CID) event

CID is a composite endpoint measuring worsening of the key clinical features of COPD, namely lung function, subject-reported outcomes, and exacerbations. CID is defined as having met at least one of the following criteria:

- ≥100 mL decrease in pre-dose/pre-BD FEV_1 (L) compared to baseline
- Decline in health-related quality of life defined as ≥4 unit increase from baseline in SGRQ total score
- Occurrence of a moderate or severe on-treatment COPD exacerbation

Time to CID event will be used as the outcome variable to explore the effect of tezepelumab and it is defined as follows:

Start date of CID event - Date of randomisation + 1

where the start date of the CID event will be the assessment date of any of the three conditions above, whichever occurs first.

Subjects will be evaluated for CID events up to Week 52. The time to CID event for subjects who complete Visit 16 (EOT) and do not experience a CID event will be censored at Visit 16. For subjects lost to follow-up, prematurely withdrawing from the study, or discontinue the study treatment and remain in the study, the time to CID event will be censored at the end of the maximum follow-up time, as described in Section 3.2.1.1.

3.2.3.3 Peripheral blood eosinophil and neutrophil counts

Absolute peripheral blood eosinophil counts and neutrophil counts are assessed by a central laboratory as a part of safety haematology testing according to the visit schedule defined in Tables 1 and 2 of the CSP.

Absolute eosinophil counts and absolute neutrophil counts along with their absolute changes from baseline, and percent changes from baseline for each post-baseline visit will be calculated as defined in Section 3.1.2 and Section 3.1.3, using conventional units (cells/μL).

3.2.3.4 Change from baseline in post-BD FEV_1 (L) at Week 52

Change from baseline in post-BD FEV_1 (L) at Week 52 will be another exploratory outcome variable and it will be derived similarly to pre-dose/pre-BD FEV_1 (L) in Section 3.2.2.5.

3.2.3.5 Exacerbations of Chronic Pulmonary Disease Tool– EXACT-PRO and E-RS™: COPD

The EXACT-PRO is a 14-item PRO instrument developed to assess the frequency, severity and duration of COPD exacerbations (Jones et al 2011, Leidy et al 2011). The instrument was developed for daily, at home, administration using a handheld electronic device. Respondents are instructed to complete the eDiary each evening just prior to bedtime and to answer the questions while considering their experiences "today" up to Week 52. The daily EXACT-PRO total score has a range of 0-100 with higher scores indicative of greater severity. Total score changes are used to identify the onset and recovery from an EXACT-PRO defined exacerbation event. In identifying event onset and recovery, the EXACT-PRO can provide information on event frequency and duration as event severity.

The number, average duration, and severity of EXACT-PRO defined events will be evaluated. EXACT-PRO daily total scores will be calculated according to the developer approved scoring algorithm. The total score will be used to identify event onset and recovery as well as the magnitude (severity) of the event. The baseline total score will be the mean score within subject over the 7 days prior to randomisation. A minimum of 4 days of data is required for calculating the baseline total score. To allow for improvement or deterioration in disease state over the course of the trial, the baseline total score will be reset every 4 weeks in the absence of an EXACT-PRO defined event. Event frequency is calculated by comparing the baseline with daily total scores. An increase in EXACT-PRO total score ≥ 9 for 3 days or ≥ 12 for 2 days indicate an event has occurred. Calculating event duration requires identification of the following 5 parameters: 1) onset; 2) 3-day rolling average; 3) maximum observed value; 4) threshold for improvement; and 5) recovery. The severity of an event is indicated by the worst (highest) EXACT-PRO total score during an event. Complete details concerning variable calculation are provided in the scoring manual (Evidera, Inc. 2014).

For the production of summary statistics, the annual EXACT-PRO defined exacerbation rate in each treatment group will be calculated using the same time-based approach as specified in Section 3.2.1.

The E-RS: COPD is an 11-item PRO developed to evaluate the severity of respiratory symptoms of COPD (Sexton et al 2010, Sexton et al 2011). The E-RS: COPD is a subset of items from the EXACT-PRO. The E-RS: COPD was designed to be captured as part of the daily EXACT-PRO assessment. Summation of E-RS: COPD item responses produces a total score ranging from 0 to 40, with higher scores indicating greater severity. In addition to the total score, symptom domain scores can be calculated for breathlessness (5 items; score range: 0–17), cough and sputum (3 items; score range: 0–11) and chest symptoms (3 items; score range: 0–12) by summing the responses of items within a respective domain. As with the total score, higher domain scores indicate greater severity.

Individual daily E-RS: COPD total and domain scores will be calculated and summarised as biweekly (14 days) means, derived by the following rules:

The biweekly mean is calculated as the sum of all non-missing daily measures/scores over 14 sequential days divided by the number of non-missing daily measures/scores. If more than 7 -daily measures/scores (>50%) within that period are missing, then the mean daily measure/score for that period is set to missing.

3.2.3.6 Other subject reported outcome variables

Daily diary metrics collected through Visit 16 (EOT) include rescue medication use, nocturnal awakening, and symptom severity questionnaire.

In the endpoints described in this section, where relevant, one day is defined as the evening measurement followed by the measurement of the following morning.

Total rescue medication use

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the subject in the eDiary twice daily. Daytime use is recorded in the evening and night-time use is recorded in the morning. Inhaler usage will be reported as the number of puffs in a given period whereas nebulizer use will be reported as the number of times.

The number of inhalations of rescue medication and nebulizer treatments captured in the eDiary each day will be calculated per subject. If a subject is missing a value for either night-time or daytime rescue medication on a given day (evening followed by morning), then the total rescue medication use for that day will be set to missing.

Total rescue medication use (inhaler and/or nebulizer), defined as the number of puffs per day will be calculated as follows:

Number of daytime inhaler puffs (recorded in the evening) + 2 x [number of daytime nebulizer times (recorded in the evening)] + number of night-time inhaler puffs (recorded the next morning) + 2 x [number of night-time nebulizer times (recorded the next morning)]

Total reliever inhaler puffs per day will be calculated as:

Number of daytime inhaler puffs (recorded in the evening) + number of night-time inhaler puffs (recorded the next morning)

Total nebulizer use (number of times) per day will be calculated as:

Number of daytime nebulizer times (recorded in the evening) + number of night-time nebulizer times (recorded in the next morning)

Biweekly mean rescue medication use (average puffs/day in total use) and change from baseline in the biweekly mean rescue medication use will be calculated.

Night awakenings

Subjects will be asked to report the occurrence of nocturnal awakenings due to COPD symptoms each morning using the electronic patient reported outcome (ePRO) device. A single question with yes/no response options will be used.

The biweekly proportion of nights with nocturnal awakenings due to COPD symptoms with non-missing night-time awakening data, and the corresponding change from baseline for each post-randomisation period will be calculated.

3.2.3.7 Healthcare resource utilisation due to COPD

COPD related healthcare resource utilisation information will be collected by the Investigator/authorized delegate at each visit as specified in the protocol and recorded in the appropriate eCRF module.

The number of days/times the following resources were utilised and the corresponding annual rates through Visit 16 (EOT) will be presented for each subject:

- Ambulance transport
- Hospitalisation, intensive care (days in intensive care)
- Hospitalisation, general care (days in general care)
- Emergency room visit (24 hrs) or urgent care
- Visit to specialist
- Visit to primary health care physician
- Other health care visit
- Home visit, physician

- Home visit, other health care
- Telephone call to physician
- Telephone call to nurse
- Telephone contact with other/health care provider

If multiple healthcare encounters are associated with one COPD exacerbation, all the encounters will be counted for this endpoint.

The annual rate of each resource utilisation through Visit 16 (EOT) will be calculated according to the formula described below:

*Annual rate of resource utilisation=Number of times*365.2 / (Last follow-up date – Visit 3 date + 1)*

3.2.3.8 Fractional exhaled nitric oxide (FeNO)

Airway inflammation will be evaluated using a standardised single-breath FeNO test in accordance with Table 1 and Table 2 of the CSP. A single exhalation technique recommended by the manufacturer will be followed (Alving et al 2017).

The FeNO test will be performed prior to spirometry.

The NIOX VERO® Airway Inflammation Monitor will be used to measure FeNO. Instructions for use of this monitor will be provided in a separate user's manual.

Change from baseline is obtained as an absolute difference between Week 52 measure and the baseline value as defined in Section 3.1.2 and Section 3.1.3. Changes from baseline at other post-baseline time points will be calculated similarly.

3.2.3.9 Biomarkers

Serum and plasma samples will be collected according to the schedule in Table 2 of the protocol to evaluate the pharmacology of tezepelumab and to evaluate changes in biomarkers related to COPD, inflammation and the thymic stromal lymphopoietin (TSLP) pathway. Baseline and early post-dose levels of serum and plasma biomarkers may also be used to explore for potential predictive biomarkers of response or exposure to tezepelumab. The specific biomarkers that may be analysed are cytokines, chemokines, and inflammatory mediators associated with COPD and the TSLP pathway. The results of exploratory biomarker analyses will not be reported in the CSR but in an addendum, or separately in a scientific report or publication.

The following biomarkers will be collected in this study:

- Total serum immunoglobulin (IgE, IgA, IgG, and IgM)

- Transcriptomic (RNA microarrays, RNA-Seq, and quantitative reverse-transcriptase polymerase chain reaction technologies)
- Nasal epithelial cell and sputum cell transcriptomics (RNA microarrays, RNA-Seq, and quantitative reverse-transcriptase polymerase chain reaction technologies), in a subset of subjects only participating in the sub-study
- Sputum induction and nasal lining fluid (cytokines, chemokines, and inflammatory mediators associated with COPD and the TSLP pathway), in a subset of subjects only participating in the sub-study
- Urine biomarkers

3.2.3.10 Genetic (DNA) sampling

A blood sample for DNA isolation will be collected at one time point only from subjects who have consented to participate in the genetic analysis component of the study.

Samples can be collected at any time after the genetic consent form is signed. The blood sample should be collected at randomisation, however, it may be taken at any visit until the last study visit. In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject.

The results of genetic analyses will not be reported in the CSR but in an addendum, or separately in a scientific report or publication.

3.3 Derivation of safety variables

3.3.1 Exposure to IP and treatment compliance

Extent of exposure to IP is defined as the number of days between the date of first dose of IP and the date of last dose of IP inclusive plus the number of days allowance for the dosing interval specified in Section 2.1.5, that is:

Extent of exposure (days) = minimum (date of last dose of IP + 33 days; date of death; date of study withdrawal) - date of first dose of IP + 1

This calculation does not consider any gaps in exposure caused by the subject missing one or more intermediate scheduled 4-weekly doses. Such cases will be identified in the CSR if they occur but will not explicitly be accounted for in any analysis.

The total subject-years exposure for a treatment group will be derived as the sum of the individual subject extents of exposure (days) for that treatment group and divided by 365.25.

Treatment compliance will be calculated as follows:

Treatment compliance (%) = (Total number of actual dosing occasions/total number of expected dosing occasions) x *100%*

In order to allow for subjects who discontinue IP early in the compliance calculation, the number of expected dosing occasions will be calculated as the number of scheduled dosing visits up to and including the last available dosing visit for that subject.

3.3.2 Adverse events (AEs) - general

AEs experienced by any subject at any time during the entire study will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be separated according to their onset date into the following study periods:

- AEs occurring during screening/run-in period: date of Visit 1 ≤ AE onset date < date of first dose of IP
- AEs occurring during on-treatment period: date of first dose of IP ≤ AE onset date ≤ minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal)
- AEs occurring during post-treatment period (for subjects still being followed up then): date of last dose of IP + 33 days < AE onset date ≤ study completion or withdrawal date
- AEs occurring during on-study period: date of first dose of IP ≤ AE onset date ≤ study completion or withdrawal date

AEs occurring during screening run-in period will be listed only.

If the AE has a completely missing (and unresolvable) onset date, then the AE will be assumed to be treatment-emergent, unless the end date indicates unambiguously that the AE resolved before treatment started. If the AE has a partially missing (and unresolvable) onset date, then the AE will also be assumed to be treatment-emergent, unless either the end date indicates unambiguously that the AE resolved before treatment started, or the partial onset date is in the month/year prior to start of treatment.

For exposure-adjusted summaries of specific AEs, the time at risk for each subject will be derived as the time during the relevant period for analysis during which the subject had no occurrence of that AE. Specifically, for on-treatment AEs, time at risk is defined as:

Time at risk (days) = minimum (date of last dose of IP + 33 days; date of death; date of study withdrawal; date of first adverse event occurrence) – date of first dose of IP + 1

The total time at risk (years) for a treatment group will be derived as the sum of the individual subject's times at risk (days) up to the first adverse event occurrence for that treatment group and divided by 365.25.

In all exposure-adjusted summaries of AEs, multiple occurrences of the same event for a particular subject will not be counted as separate events. A subject will either be considered to have no events of the type being summarised, or one or more occurrences of that event.

3.3.3 Adverse events of special interest

The protocol specifies Adverse Events of Special Interest (AESIs) as those which merit special attention in this trial, and for which derivation details (for those derived from the eCRF), or a statement when the derivation needs to be referenced externally to the SAP (for those derived from MedDRA dictionary terms), are given in Appendix 8.1.

Similar considerations apply to any additional supporting analysis of AESIs, in which MedDRA dictionary-based definitions are used.

3.3.4 Laboratory variables

Clinical chemistry, haematology and urinalysis will be performed by a central laboratory according to the schedule and the variable specifications described in the CSP. Urine samples will be analysed locally and sent for analysis at the central laboratory only if a positive dipstick result for any parameter is observed.

Changes from baseline in continuous laboratory variables will be calculated at relevant visits as specified in Section 3.1.2 and Section 3.1.3.

In all analysis of continuous laboratory variables, any value recorded only as below Lower Limit of Quantification (LLOQ) will be set to LLOQ and included in the analysis. Any value recorded only as above Upper Limit of Quantification (ULOQ) will be set to ULOQ and included in the analysis. Absolute values will be compared to the relevant normal reference range, as provided by the central laboratory, and classified as low (below range), normal (within range or on the limits) or high (above range). All values (absolute and change) falling outside the normal reference ranges will be flagged. These classifications will also be used for shift tables.

For the purposes of shift tables, baseline will be defined as specified in Section 3.1.2. Minimum, maximum and last values calculated across all visits in the relevant study period will use all available values including those from unscheduled and repeat visits, and irrespective of whether the values have been selected for use in summaries using visit windows (see Section 3.1.5).

Urinalysis data will be categorised as negative (0), positive (+), or strongly positive (++, +++, or >+++) at each time-point.

Liver function tests will also be evaluated as multiples of the upper limit of the normal reference range (ULN). Subjects who meet any of the following criteria at any time during the study will be flagged:

- Aspartate aminotransferase (AST) ≥ 3 x ULN
- Alanine aminotransferase (ALT) ≥ 3 x ULN
- Total bilirubin (TBL) ≥ 2 x ULN

Other multiples of ULN will also be used in the display of liver function tests.

3.3.5 Vital signs

Pre-dose vital signs (pulse rate, systolic blood pressure (BP), diastolic BP (DBP), respiratory rate, body temperature, supplemental O_2 status, oxygen saturation (SpO_2)) will be obtained in accordance with the schedule provided in CSP Table 1 and Table 2.

BMI is calculated as: $BMI = Weight\ (kg) / [Height\ (m)]^2$

Changes in vital sign variables between baseline and each scheduled assessment will be calculated at relevant clinic visits as specified in Section 3.1.2 and Section 3.1.3.

Absolute values and changes from baseline (where applicable) will be compared to the relevant reference range tabulated below, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the reference ranges will be flagged.

Table 3 Vital signs reference ranges				
Parameter	**Standard Units**	**Lower Limit**	**Upper Limit**	**Change from Baseline Criteria**
Diastolic Blood Pressure (sitting)	mmHg	60	100	±15
Systolic Blood Pressure (sitting)	mmHg	90	160	±30
Pulse Rate (sitting)	Beats/min	50	100	±20
Respiratory Rate	Breaths/min	8	20	
Body Temperature	Celsius	36.0	37.5	
Oxygen Saturation (SpO_2)	%	90	101	

3.3.6 Twelve lead electrocardiogram (ECGs)

12-lead digital ECG measurements will be recorded in accordance with the protocol, with the baseline visit being defined as any time between Visit 1 and Visit 2 inclusive.

The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

3.3.7 Smoking status

Smoking status will be assessed at every visit starting from enrolment (Visit 1) until the end of the last Follow up Visit (Week 64) by collecting the subject's response to a single yes/no question from study personnel: 'What is your smoking status as of today, do you currently smoke? Any change in smoking status between Visit 1 (enrolment) to Visit 3 (randomisation) will result in a screen failure. Smoking status changes during Visit 3 to the end of the last Follow up Visit (Week 64) will be captured on the eCRF but the subject will be permitted to continue in the study.

3.4 Derivation of pharmacokinetic and immunogenicity variables

The third-party vendor analysing the PK samples will be unblinded to the randomised treatment assignments of all subjects; no one from the study team will have access to the PK or ADA data until after the study has been unblinded.

3.4.1 Pharmacokinetic variables

Serum samples will be collected at specified time points according to the schedule of assessment for determination of tezepelumab concentrations. Serum trough tezepelumab concentrations in the tezepelumab group will be summarised by time point.

The assay for determination of tezepelumab concentrations will only be performed using samples for subjects randomised to tezepelumab. Subjects who are randomised to placebo will not have their PK samples analysed by the vendor laboratory.

3.4.2 Immunogenicity variables

Serum samples for determination of tezepelumab concentration and the presence of ADA and neutralizing antibodies (nAb) will be collected at baseline prior to first IP administration, at multiple time point before IP administration during the treatment period, and at selected timepoints in the follow-up period, according to the CSP schedule of assessment.

Samples will be used to determine tezepelumab concentrations, and to measure the presence of ADA and nAb, according to validated assays performed by a designated third-party vendor. Samples that are confirmed positive for ADAs will be further analysed for the presence of nAb.

4. ANALYSIS METHODS

4.1 General principles

4.1.1 Statistical hypotheses for primary efficacy variables

The null hypothesis is that the exacerbation rate on tezepelumab is greater than or equal to the exacerbation rate on placebo. The alternative hypothesis is that the exacerbation rate on tezepelumab is less than the exacerbation rate on placebo, i.e.

$$H_0: \text{Rate ratio (tezepelumab vs Placebo)} \geq 1$$
$$H_a: \text{Rate ratio (tezepelumab vs Placebo)} < 1$$

4.1.2 Multiple testing procedure

In this Phase 2a study, in order to describe the nature of the benefits with tezepelumab and to define study success, the primary endpoint will be tested using a one-sided 5% significance level. In addition, and although not powered, the primary endpoint will also be tested using a one-sided 2.5% alpha in order to strongly control type I error. No additional adjustment for multiplicity will be implemented and all additional reported p-values will be considered nominal.

4.2 Analysis methods

4.2.1 Subject disposition, demography, and baseline characteristics

Subject disposition will be summarised using the all subjects analysis set. The number of enrolled subjects and those not randomised (and reason) will be summarised. The number and percentage of subjects within each treatment group will be presented by the following categories; randomised, received IP, did not receive IP (and reason), completed treatment, discontinued treatment (and reason), completed study (subjects who completed IP and study, and subjects who discontinued IP but completed study assessments), and discontinued study (including reason). All randomised subjects will be used as the denominator in percentage calculations for the applicable categories above.

Subject recruitment by country and centre will also be summarised for subjects in the FAS.

Disposition will also be provided for the number and percentage of randomised subjects who consented separately to participate in the optional sub-studies (e.g. DNA sampling, sputum and nasal lining fluid/epithelial cells sub studies).

The number of subjects in each of the analysis sets defined in Section 2.1 will be presented.

The number and percentage of subjects, who discontinued IP, but remained in the study will be presented by treatment group and option of follow up (Section 1.2) at each scheduled timepoint.

Kaplan-Meier plots will be produced summarising separately the time (in days) to premature discontinuation of IP and withdrawal from the study. In both cases, subjects without the premature event will be censored at Week 52.

Demographic data such as age, gender, and race will be summarised by treatment group for subjects in the FAS. All subgroups as defined in Section 3.1.7 will be summarised by treatment group for subjects in the FAS. In addition, the screening blood eosinophil category ≥150/μL will be further categorised as ≥150 - 300/μL, and ≥300/μL and summarised by treatment group.

Various baseline characteristics will also be summarised for the FAS by treatment group, which include respiratory disease history, subject characteristics (weight, height and BMI), nicotine use and consumption, baseline lung function (pre- and post-BD FEV_1 (L), FEV_1 (% PN), FVC (L), FVC (% PN), and FEV_1/FVC). The number of historic COPD exacerbations will be plotted.

Stratification factors recorded at randomisation by the IWRS and by eCRF will be summarised by treatment group for the FAS.

Medical and surgical history will be summarised by MedDRA Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA for subjects in the FAS by treatment group. Medical history will be presented separately as current (defined as ongoing at screening) and past (not ongoing at screening).

Important PDs will be summarised by treatment group for subjects in the FAS. COVID-related and non-COVID-related will also be reported separately.

4.2.2 Prior and concomitant medications

The number and percentage of subjects receiving each medication (by ATC classification system codes and generic name) will be presented by treatment group for subjects in the FAS. Separate tables will be presented for allowed and disallowed medications received during each of the following periods as defined in Section 3.1.4: Prior, Concomitant (on-treatment), Concomitant (post-treatment). Disallowed medications will include medications defined as prohibited according to Section 6.5 of the CSP. They will be defined following a physician review (prior to database lock) of the unique combinations of ATC code classifications and generic terms captured.

Tables for baseline maintenance medications (started prior to and ongoing after the first day of IP) will be produced. The number and percentage of patients taking maintenance COPD medications at baseline will be summarised. Summary statistics will be provided for ICS doses, converted to their Fluticasone

Propionate equivalent in micrograms. The number of patients treated with ICS at baseline will be summarised by ATC code and preferred term, with total daily dose (non-converted) at baseline summarised for each preferred term. The total number of days of systemic corticosteroid treatment associated with COPD exacerbations per subject from the first day of IP up to Week 52 will be summarised for the FAS. Prior biologic use for COPD (started prior to V1 and stopped prior to treatment), including those received through a clinical trial where the actual treatment allocation is unknown, will be summarised separately.

Medications will be classified using the latest version of the WHO Drug Dictionary.

Percentages will be calculated relative to the number of subjects in the FAS.

Data from subjects who discontinued IP, regardless of level of follow up chosen will, where possible and relevant, be included in the appropriate medication summaries.

4.2.3 Exposure and compliance

Exposure and treatment compliance derivation details are defined in Section 3.3.1.

Extent of exposure to IP, total duration of study treatment administration (days), total subject-year exposure, compliance, and total number of dosing occasions will be summarised by treatment group, for subjects in the safety analysis set.

4.2.4 Primary outcome variables

4.2.4.1 Primary analyses

The primary efficacy variable is the annual rate of moderate or severe COPD exacerbations up to Week 52 and the primary analysis is to compare the annual COPD exacerbation rate of tezepelumab with placebo. Subjects will be analysed using the full analysis set according to randomised treatment.

The null hypothesis is that the exacerbation rate on tezepelumab is greater than or equal to the exacerbation rate on placebo. The alternative hypothesis is that the exacerbation rate on tezepelumab is less than the exacerbation rate on placebo, i.e.

H_0: Rate ratio (tezepelumab vs Placebo) ≥ 1
H_a: Rate ratio (tezepelumab vs Placebo) <1

Annual exacerbation rate in the tezepelumab group will be compared to annual exacerbation rate in the placebo group using a negative binomial model for the primary analysis. The response variable in the model will be the number of COPD exacerbations experienced by a subject during the follow-up for exacerbations. The model will include covariates of treatment group, region, and the number of exacerbations reported at randomization as recorded in IWRS (2, ≥3). The logarithm of the subject's

corresponding time at risk will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events occur.

Two separate negative binomial regression models will be generated for the primary analysis for the following estimands:

- **Primary estimand**:
    - **Population** - subjects with moderate to very severe COPD who are randomised and receive at least one dose of IP
    - **Variable** - annual rate of moderate or severe COPD exacerbations up to Week 52
    - **Population-level summary measure** – exacerbation rate ratio of tezepelumab versus placebo
    - **Handling of intercurrent events**:
        - Treatment discontinuation: All available data are used regardless of whether treatment discontinuation occurs;
        - Use of an alternative biologic: All available data are used regardless of whether subject switches to an alternative biologic therapy.
- **Supplemental estimand**:
    - **Population** - subjects with moderate to very severe COPD who are randomised and receive at least one dose of IP
    - **Variable** - annual rate of moderate or severe COPD exacerbations up to Week 52
    - **Population-level summary measure** – exacerbation rate ratio of tezepelumab versus placebo
    - **Handling of intercurrent events**:
        - Treatment discontinuation: All available data are used up until randomised treatment is discontinued;
        - Use of an alternative biologic: All available data are used up until subject switches to an alternative biologic therapy.

The COPD exacerbation rate and the corresponding 90% confidence interval (CI) within each treatment group will be presented. The estimated treatment difference from placebo (i.e. the absolute difference between tezepelumab and placebo, and the rate ratio of tezepelumab versus placebo), corresponding 90% CI, and 1-sided p-value for the ratio will be presented. The 95% CI, and 2-sided p-value for the rate ratio will also be presented. Marginal standardisation methods will be used on the model estimates for all negative binomial analyses, unless otherwise specified.

The negative binomial model under the primary estimand will be repeated for the following, as a supportive analysis to the primary:

- Excluding moderate exacerbations treated with antibiotics alone.

COPD exacerbation summary statistics will be presented based on the full analysis set by treatment group. The individual exacerbation criteria (use of systemic corticosteroids, use of antibiotics, and inpatient hospitalisation or death due to COPD) will also be summarised descriptively. Exacerbations with an alert triggered by ≥2 major symptoms, 1 major plus ≥1 minor symptom and investigator justified exacerbations will be summarised by severity and treatment group for the FAS. A bar chart showing the percentage of subjects by number of COPD exacerbations over 52 weeks will also be presented.

4.2.4.2 Sensitivity analyses to primary endpoint

Additional sensitivity analyses to assess the robustness of the primary analysis results to missing data are outlined in Appendix 8.2 and to assess the impact of COVID-19 on primary analysis results in Appendix 8.4 .

4.2.4.3 Subgroup analyses for primary endpoint

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses and statistical modelling including testing for interaction between treatment and covariates will be performed for subjects in the FAS for all the factors listed in Section 3.1.7.

For each of the subgroup factors, a separate negative binomial regression model will be fitted using the same model terms as used for the primary analysis (described in Section 4.2.4.1), with additional terms for the subgroup main effect and the treatment by subgroup interaction. Region and prior exacerbation count are not included as a covariate if they are the subgroup factor. Imbalanced subgroups which cause convergence issues may be excluded from the analysis.

Similar outputs will be presented for each subgroup as for the primary analysis. The p-value for the interaction term by each treatment group will be presented in the summary tables and forest plots with 95% CI displayed.

It is important to note that the study has not been designed or powered to assess efficacy within any of these pre-defined subgroups, and as such these analyses are considered as exploratory.

4.2.5 Secondary outcome variables

Analyses of secondary outcome variables will handle intercurrent events as per the primary estimand, unless otherwise stated.

4.2.5.1 Time to first COPD exacerbation

Time to first COPD exacerbation over the 52-week treatment period will be analysed to explore the extent to which treatment with tezepelumab delays the time to first exacerbation compared to placebo. A Cox proportional hazard model will be fitted to the data with covariates of treatment, region and number of exacerbations recorded at randomization in IWRS (2, ≥3). Results will be summarised as hazard ratio for tezepelumab versus placebo with the 95% CI and p-value.

Time to first COPD exacerbation will also be displayed graphically using a Kaplan-Meier plot.

The number of subjects who are exacerbation free up to Week 52 will be summarised for each treatment group together with the censoring rate. The time to first exacerbation up to Week 52 will be summarised by minimum, maximum and percentiles (25^{th}, median, 75^{th}) with their corresponding 95% CIs using Kaplan-Meier technique. The probability of exacerbation free by Week 24 and Week 52 and their 95% CI, estimated using the Kaplan-Meier technique, will also be reported.

4.2.5.2 Proportion of subjects exacerbation free at Week 52

The proportion of subjects exacerbation free at Week 52 in the tezepelumab group will be compared to the proportion in the placebo group using a logistic regression model with region and number of exacerbations recorded at randomization in IWRS (2, ≥3) as covariates.

The results of the analyses will be presented as an odds ratio, together with associated 95% CI and 2-sided p-value. The number and percentage of subjects exacerbation free at Week 52 will also be summarised by randomised treatment group for subjects in the FAS.

4.2.5.3 Annual rate of severe COPD exacerbations

Annual rate of severe COPD exacerbations up to Week 52 will be analysed using a similar negative binomial model as outlined for the primary efficacy variable in Section 4.2.4.1 under the primary estimand only (for handling of intercurrent events) and with additional sensitivity analyses to assess the robustness of the results to missing data as outlined in Appendix 8.2.

The annual severe COPD exacerbations rate and the corresponding 95% CI within each treatment group will be presented. The estimated treatment difference from placebo (i.e. the absolute difference between tezepelumab and placebo, and the rate ratio of tezepelumab versus placebo), corresponding 95% CI, and 2-sided p-value for the ratio will be presented. Marginal standardisation methods will be used on the model estimates for all negative binomial analyses, unless otherwise specified.

If any notable differences in treatment effect are seen by subgroups for the primary endpoint, analyses of severe exacerbations in those subgroups may be conducted.

4.2.5.4 Time to first severe COPD exacerbation

Time to first severe COPD exacerbation through Week 52 will be analysed using a similar model for time to first COPD exacerbation as in Section 4.2.5.1.

4.2.5.5 Change from baseline in pre-dose/pre-BD FEV_1 (L) at Week 52

Change from baseline in pre-dose/pre-BD FEV_1 (L) at Week 52 will be compared between tezepelumab and placebo using a repeated measures analysis on subjects with a baseline pre-dose/pre-BD FEV_1 (L) and at least one non-missing post-randomisation pre-dose/pre-BD FEV_1 (L) value for subjects in the FAS. The dependent variable will be the change from baseline in pre-BD FEV_1 (L) at post-baseline protocol-specified visits (up to the EOT visit). Treatment group will be fitted as the explanatory variable, while region, prior exacerbation count as recorded in IWRS (2, ≥3), visit, baseline pre-dose/pre-BD FEV_1 (L), and the interaction between visit and treatment will be fitted as covariates. Visit will be fitted as a categorical variable, subject will be included in the model using the REPEATED statement (not the RANDOM statement), and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance covariance matrix will be used instead. If the procedure fails to converge with both variance-covariance matrices above, then drop out of covariates will be considered. The Kenward-Roger method will be used in the model to calculate the denominator degrees of freedom, i.e. DDFM=KR. The model is:

*Change in pre-dose/*pre-BD FEV_1 (L) =*Treatment group*+ *baseline pre-dose/*pre-BD FEV_1 (L) + *region* + *prior exacerbation strata* + *visit* + *treatment*visit*

This model will be used in two separate Mixed Model Repeated Measures model (MMRM) analyses [assuming missing at random (MAR)], namely:

- The primary analysis will handle intercurrent events as per the primary estimand.
- The supplemental analysis will handle intercurrent events as per the supplemental estimand.

Results will be presented in terms of LSMEANS (with the OBSMARGIN option added), treatment differences in LSMEANS, 95% CI, and p-values for all visits.

Summary statistics of the change from baseline in pre-dose/pre-BD FEV_1 (L) at the study site will be produced by treatment group and visit.

Additional sensitivity analyses to assess the robustness of the repeated measures analysis for pre-dose/pre-BD FEV_1 to missing data are outlined in Appendix 8.2.

Subgroup analyses of the change from baseline in pre-dose/pre-BD FEV_1 will be conducted for the subgroup factors listed in Section 3.1.7 based on FAS. The analyses will use the same MMRM model described above with additional terms for the subgroup main effect and the interaction among treatment, subgroup and visit. The model of each subgroup will be:

*Change in pre-dose/*pre-BD FEV_1 (L) =*Treatment group+ baseline pre-dose/*pre-BD FEV_1 (L) + *region (if not subgroup)+ prior exacerbation strata (if not subgroup) + visit + treatment*visit + subgroup + treatment* subgroup + subgroup* visit + treatment* subgroup*visit*

Region and prior exacerbation count at randomisation are not included as a covariate if they are the subgroup factor of interest. Imbalanced subgroups which cause convergence issues may be excluded from the analysis.

Similar outputs will be presented for each subgroup as for the change from baseline in pre-dose/pre-BD FEV1 (L). The p-value for the interaction term by each treatment group will be presented in the summary tables and a forest plot will present the difference in LSMEANS with 95% CI intervals for each level of the subgroups.

4.2.5.6 St. George's Respiratory Questionnaire (SGRQ)

Changes from baseline in SGRQ total score at Week 52 will be analysed using a similar model (MMRM) for change from baseline in pre-dose/pre-BD FEV_1 (L) in Section 4.2.5.5, with the appropriate baseline value used in the model.

Results will be presented in terms of LSMEANS (with the OBSMARGIN option added), treatment differences in LSMEANS, 95% CI, and p-values for all visits. The results at Week 52 will be of primary interest.

The individual component scores and SGRQ total scores and changes from baseline will be summarised by treatment group and visit.

The cumulative distribution function of absolute changes from baseline in SGRQ total score at Week 52 will be also plotted in a figure.

The proportion of subjects in terms of SGRQ total score response status (improvement, worsening, no change, and not evaluable) at Week 52 will be summarised descriptively by treatment group.

Additional sensitivity analyses to assess the robustness of the repeated measures analysis for SGRQ to missing data are outlined in Appendix 8.2.

Subgroup analyses of the change from baseline in SGRQ total score will be conducted for the subgroup factors listed in Section 3.1.7 based on FAS. The analyses will use the same MMRM model described in Section 4.2.5.5 with additional terms for the subgroup main effect and the interaction among treatment, subgroup and visit. The model of each subgroup will be:

Change from baseline in SGRQ total score =Treatment group+ baseline SGRQ *+ region (if not subgroup)+ prior exacerbation strata (if not subgroup) + visit + treatment*visit + subgroup + treatment* subgroup + subgroup* visit + treatment* subgroup*visit*

Region and prior exacerbation count are not included as a covariate if they are the subgroup factor of interest. Imbalanced subgroups which cause convergence issues may be excluded from the analysis.

Similar outputs will be presented for each subgroup as for the change from baseline in SGRQ total score. The p-value for the interaction term by each treatment group will be presented in the summary tables and a forest plot will present the difference in LSMEANS with 95% CI intervals for each level of the subgroups.

4.2.5.7 Proportion of subjects achieving a decrease of ≥4-points in SGRQ total score at Week 52 (MCID)

The proportion of subjects achieving a MCID of ≥4-units decrease from baseline in SGRQ total score at Week 52 (i.e. responders) in the tezepelumab group will be compared with the proportion in the placebo group using a similar logistic regression model as that used for the proportion of subjects exacerbation-free at Week 52 in Section 4.2.5.2. The baseline SGRQ score will be included as a covariate in this model.

The results of the analysis will be presented as an odds ratio, together with associated 95% CI and 2-sided p-value. The number and percentage of subjects achieving a MCID will also be summarised by treatment group for subjects in the FAS.

As a sensitivity analysis, for subjects who completed the study but have a non-evaluable SGRQ total score change at Week 52 due to missing Week 52 data, the Week 52 assessment will be imputed with the last non-missing post-baseline value (last observation carried forward (LOCF) method) and

responder status will be re-evaluated. A similar logistic regression model as above will be used to compare the proportions of responders as sensitivity analysis.

4.2.5.8 COPD assessment tool (CAT)

The CAT total scores and changes from baseline will be summarised by treatment group and visit.

Change from baseline in CAT score through Week 52 will be analysed using a similar model (MMRM) as for the change from baseline in pre-dose/pre-BD FEV1 (L) described in Section 4.2.5.5. Results will be presented in terms of LSMEANS (with the OBSMARGIN option added), treatment differences in LSMEANS, 95% CI, and p-values for all visits.

4.2.5.9 Additional supportive endpoints to secondary

The proportion of subjects with ≥1 severe COPD exacerbation over 52-weeks treatment will be analysed similarly to the proportion of subjects exacerbation free at Week 52 in Section 4.2.5.2.

4.2.6 Exploratory outcome variables

All continuous exploratory endpoints will be summarised descriptively and analysed under a MAR assumption using an MMRM model analogous to that specified for the secondary endpoints in Section 4.2.5.5 and handling intercurrent events as per the primary estimand.

The following is proposed for the exploratory endpoints:

- Change from baseline and percent change from baseline in blood eosinophil and neutrophil levels summarised descriptively
- Change from baseline in post-BD FEV_1 (L) analysed using MMRM and summarised descriptively
- Change from baseline in E-RS^{TM}: COPD total score and domain scores analysed using MMRM and summarised descriptively
- Change from baseline in FENO analysed using MMRM and summarised descriptively

Results of MMRM analyses will be presented in terms of LSMEANS (with the OBSMARGIN option added), treatment differences in LSMEANS, 95% CI, and p-values for all visits.

Summary statistics of the EXACT-PRO event frequency, duration, and severity will be produced by treatment group.

Annual rate of EXACT-PRO defined exacerbation will be analysed using the method described for the primary analysis in Section 4.2.4.1 for subjects in the full analysis set. 95% CI will be presented for annual exacerbation rate, absolute difference, and the rate ratio.

All time to event exploratory endpoints will be analysed by using the same Cox proportional hazard model as in Section 4.2.5.1, and will be displayed graphically using a Kaplan-Meier plot.

This analysis includes the following endpoints:

- Time to first COPDCompEx event over 12-weeks
- Time to CID event over 52 weeks-treatment

COPDCompEx rates in the tezepelumab group will be compared to those seen in the placebo group using a negative binomial model, similarly to the primary analysis under the primary estimand in Section 4.2.4.1. The response variable in the model will be the number of COPDCompEx events experienced by a subject over the first 12 weeks of treatment period as well as over the entire 52 week treatment period. Treatment, region, and number of exacerbations at randomization as recorded in IWRS (2, ≥3) will be included as covariates in this model. The logarithm of subject's time at risk (in years) for a COPDCompEx event will be used as an offset variable in the model, to adjust for subjects having different follow-up times during which the events occur (noting that the maximum follow up time is to Visit 6 (week 12) and Visit 16 (and Week 52)). For all further derivation details, see Section 3.2.3.1. The estimated treatment difference from placebo (i.e. the absolute difference between tezepelumab and placebo, and the rate ratio of tezepelumab versus placebo), corresponding 95% CIs, and 2-sided p-value for the ratio will be presented. Descriptive summaries of the COPDCompEx events will also be presented. A bar chart showing the percentage of subjects by number of COPDCompEx events over 12 weeks and 52 weeks will also be presented.

The annual rate of each resource utilisation through Week 52 in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model, similarly to the primary analysis under the primary estimand in Section 4.2.4.1. The response variable in the model will be the number of times of each COPD specific resource utilisation items as listed in Section 3.2.3.7. The logarithm of the subject's corresponding follow-up time as defined in Section 3.2.1.1 will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events occur. The estimated treatment difference from placebo (i.e. the absolute difference between tezepelumab and placebo, and the rate ratio of tezepelumab versus placebo), corresponding 95% CIs, and 2-sided p-value for the ratio will be presented. The number and percentage of subjects with COPD specific resource utilisation, specified in Section 3.2.3.7, and overall annual rate during the treatment period will be summarised by treatment group for subjects in the FAS. The total number of days/times and annual rate of each specific resource utilisation at a subject level will be summarised by descriptive statistics.

Sensitivity and subgroup analyses will not be performed on exploratory endpoints.

4.2.6.1 Other subject reported outcome variables

Total rescue medication use

Total rescue medication use and the number of nights with awakening and their change from baseline will be summarised by treatment and visit for subjects in the FAS.

Change from baseline in total rescue medication use will be analysed using the same MMRM method for pre-dose/pre-BD FEV_1 (L) as described in Section 4.2.5.5. Results will be presented in terms of LSMEANS (with the OBSMARGIN option added), treatment differences in LSMEANS, 95% CI, and p-values for all visits.

Nights with awakening due to respiratory symptoms

The number of nights with awakening and change from baseline will be summarised by treatment and visit.

Change from baseline in the proportion of nights with awakening due to COPD awakening will be analysed using the same MMRM method for pre-dose/pre-BD FEV_1 (L) as described in Section 4.2.5.5. Results will be presented in terms of LSMEANS (with the OBSMARGIN option added), treatment differences in LSMEANS, 95% CI, and p-values for all visits.

4.2.6.2 Biomarkers

Biomarker serum TSLP results and plasma Fibrinogen results and changes from baseline will be summarised by treatment and visit.

Other biomarkers and the results of any investigation will be reported separately in a scientific report or publication and analyses covered by a separate SAP.

4.2.6.3 Genetic (DNA) sampling

The results of any investigation will be reported separately in a scientific report or publication and analyses covered by a separate SAP.

4.2.7 Safety and tolerability

All safety variables will be summarised using the safety analysis set (see Section 2.1.2 for details).

4.2.7.1 Adverse events

AEs will be summarised separately for the on-treatment and on-study periods, as defined in Section 3.1.4 unless stated otherwise. All AE summaries will be presented by treatment group. AEs occurring

during the screening/run-in period, or occurring post-treatment will be listed, but not summarised separately.

An overall summary table will be produced showing the number and percentage of subjects with at least one AE in each of the following categories: any AEs, SAEs, AEs with a fatal outcome, and AEs leading to discontinuation of IP (DAEs). The total number of AEs in the different AE categories will also be presented as well as the number of subjects (i.e. accounting for multiple occurrences of the same event in a subject).

All AEs will be summarised by SOC and PT assigned to the event using the MedDRA dictionary. For each PT, the number and percentage of subjects reporting at least one occurrence of the event will be presented (i.e. subjects with multiple occurrences of the same PT will only be counted once).

Similar summaries by SOC and PT will also be presented for:

- SAEs
- AEs with a fatal outcome
- DAEs
- DAEs casually related to IP
- SAEs leading to discontinuation of IP
- Each AESI category separately
- The most common AEs (defined as those occurring in >3% of subjects in either treatment group) by PT only

All AEs (by PT) will be summarised additionally by causality and maximum intensity. If a subject reports multiple occurrences within each PT, the maximum intensity will be taken as the highest recorded (the order being mild, moderate, and severe) respectively.

Separate listings of subjects with AEs, SAEs, AEs with a fatal outcome, DAEs, SAEs leading to discontinuation of IP, and severe infections will be presented.

Exposure-adjusted AE summaries will be presented by SOC and PT for each of the following (on-treatment summaries only):

- All AEs
- SAEs

- Each AESI separately

In these summaries, the exposure-adjusted rate will be defined for each treatment as the number of subjects in that treatment group reporting the AE divided by the total time at risk for all subjects in that treatment group, the latter as defined in Section 3.3.2. Rates will be reported as events per 100 subject-years.

Events confirmed by the independent adjudication committee (major adverse cardiac events (MACE) and malignancies) will be summarised by treatment group.

4.2.7.2 Laboratory data

All continuous laboratory variables will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. These summaries will be produced for the on-study period as defined in Section 3.1.4. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean, and standard deviation (SD).

Central laboratory normal reference ranges will be used for the identification of individual clinically important abnormalities. A shift table will be produced for each laboratory variable to display low, normal, and high values. The shift tables will present baseline and maximum/minimum/last post-baseline values for each variable.

Shift plots showing each individual subject's laboratory value at baseline and at maximum/ minimum/ last value post-baseline will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points then shift plots of these data may be produced. The diagonal line of no change, and horizontal and vertical reference lines indicating the limits of the normal reference ranges, will also be displayed on the shift plots.

Both shift tables and shift plots will be produced using all data for the on-study period, as defined in Section 3.1.4.

The frequencies of clinically noteworthy values (using normal reference ranges) occurring during the study will also be given.

In order to identify potential Hy's Law cases, maximum post-baseline TBL will be plotted separately against both maximum post-baseline ALT and AST, expressed as multiples of ULN. These plots will be produced on a log scale, with reference lines included at 2xULN for TBL, and at 3xULN for both ALT and AST. These plots will be produced using all data for the on-study period.

For all subjects who meet the biochemical criteria for Hy's Law (potential Hy's Law cases), the relevant laboratory variables will be tabulated showing all visits for these subjects.

Subjects with elevated ALT or AST in addition to elevated TBL at any time may be explored further graphically using individual subject profile plots.

For urinalysis data, a shift table will be generated to present changes from baseline to maximum/last value post-baseline. All data for the on-study period will be used.

Any data outside the central laboratory reference ranges will be explicitly noted on the listings that are produced.

Microbiology data will be listed.

4.2.7.3 Vital signs

All vital signs variables will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. These summaries will be produced for the on-study period. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean, and SD.

AZ-defined reference ranges (see Section 3.3.5) will be used for the identification of individual abnormalities. A shift table will be produced for each vital sign variable to display low, normal, and high values. The shift tables will present baseline and maximum/minimum/last post-baseline values for each variable.

Shift plots showing each individual subject's vital sign value at baseline and at maximum/minimum/last value post-baseline will be produced for each continuous vital sign variable.

Both shift tables and shift plots will be produced using all data for the on-study period.

Subjects who have treatment-emergent changes from baseline outside the pre-defined AZ clinically important change criteria in Section 3.3.5 will be presented. All data for the on-study period will be used.

4.2.7.4 Twelve lead electrocardiogram (ECGs)

A shift table will be produced for each ECG parameter to display normal, abnormal – not clinically significant, abnormal - clinically significant, and not done. The shift tables will present baseline and last observation post-baseline value.

4.2.7.5 Smoking status

Smoking status changes will be summarised by treatment group and visit for subjects in the safety analysis set during on-study period. A shift table will be produced to display current, former smoker and missing. The shift tables will present baseline and last observation post-baseline value.

4.2.8 Pharmacokinetics and immunogenicity

4.2.8.1 Analysis of pharmacokinetics

PK variables will be summarised using pharmacokinetics (PK) analysis set as defined in Section 2.1.3.

Serum samples for PK are scheduled to be collected at weeks 0, 4, 12, 24, 36, 52, 64 and at the premature IP discontinuation visit, where appropriate. Data will be assigned to weeks based on the windows defined in Section 3.1.5.

The following criteria will also apply for data to be included in the summary table:

- Only pre-dose samples at Week 0.
- Only pre-dose samples at Weeks 4, 12, 24 and 36 that were also between ≥ 21 and ≤ 35 days post the previous dose.
- Only samples that were taken between ≥ 21 and ≤ 35 days post the previous dose for Week 52.
- All samples for Week 64 that were taken within the visit window defined in Section 3.1.5.

For descriptive statistics of tezepelumab concentrations:

- If, at a given time point, 50% or less of the concentrations are non-quantifiable (NQ), the geometric mean, coefficient of variation (CV), arithmetic mean, and SD will be calculated by substituting the lower limit of quantification (LLOQ) divided by 2 for values which are NQ.
- If more than 50%, but not all, of the concentrations are NQ, the geometric mean, CV, arithmetic mean, and SD will be reported as not calculable (NC).
- If all the concentrations are NQ, the geometric mean and arithmetic mean will be reported as NQ and the CV and SD as NC.
- The median, minimum and maximum will also be reported.

The LLOQ of tezepelumab in serum will be 0.010 µg/mL.

Observed serum concentrations of tezepelumab for each individual will be listed by visit to confirm tezepelumab administration.

The PK data may be merged with those from other clinical studies for a population-based meta-analysis. If performed, results of the meta-analysis will be presented in a separate pharmacometrics report outside of the CSR, and this is not considered further in this SAP.

4.2.8.2 Analysis of immunogenicity

All analyses of immunogenicity variables will be based on the safety analysis set as defined in Section 2.1.2.

The number and percentages of ADA-positive subjects at each visit will be summarised by treatment group during the on-study period. Descriptive statistics including number of subjects, Q1 median, Q3 and range of the actual ADA titres by treatment group and visit, where possible, will be provided.

The ADA status across the study for each subject will also be classified and summarised by treatment group. Specifically, the following ADA results will be evaluated as number and proportion of subjects in cohorts together with corresponding titre summaries. However, if the number of ADA positive subjects in the safety analysis set is small, then the ADA variables may be listed only in the CSR:

- Subjects who are ADA positive at any time including baseline (ADA prevalence).
- Subjects who are baseline ADA positive.
- Subjects who are only baseline ADA positive.
- Subjects who are any post-baseline ADA positive.
- Subjects who are both ADA positive at baseline and positive in at least one post baseline measurement.
- Subjects who are ADA positive post-baseline and ADA negative at baseline (treatment-induced ADA).
- Subjects with treatment-boosted ADA, defined as baseline positive ADA titre that was boosted to a 4-fold or higher-level following IP administration.
- Subjects with treatment emergent ADA (ADA incidence): defined as the sum of treatment-induced ADA and treatment-boosted ADA.
- Subjects who are persistently positive; persistently positive is defined as at least 2 post-baseline ADA positive measurements (with ≥ 16 weeks between first and last positive) or an ADA positive result at the last available post-baseline assessment.
- Subjects who are transiently positive; transiently positive is defined as at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.

For ADA summaries at a single time point (e.g. baseline ADA or by visit) the corresponding titre summary will be based on the titre of the positive sample for that particular visit. For proportions summarising across visits (e.g. any ADA post-baseline) the corresponding titre summaries will be based on the maximum titre of all positive samples for each subject.

Neutralizing ADA evaluations will be conducted on confirmed ADA positive samples. The test sample is deemed positive or negative for the presence of nAb to tezepelumab relative to a pre-determined (in assay validation) statistically derived cut point. The number and proportion of subjects who are nAb positive at any time will be evaluated.

The potential effects of ADA status and ADA titer on pharmacokinetics of tezepelumab will be evaluated. The potential association of immunogenicity with efficacy and safety may be evaluated, if appropriate.

5. INTERIM ANALYSES

A data cut off for an interim analysis to potentially stop the study due to futility of efficacy was originally planned to occur when 182 subjects had been randomised. As a result of the pause in recruitment due to COVID-19, the futility analysis is now planned to occur when approximately 30% of information has been achieved. An Independent Data Monitoring Committee (IDMC) will be used. Futility will be declared if the lower bound of an 80% confidence interval for the exacerbation rate ratio of tezepelumab vs. placebo is greater than 0.80. The futility boundary and method of assessing futility was chosen based on the operating characteristics of ~33% chance of stopping the study under the null hypothesis and ~4% chance of stopping the study assuming an exacerbation rate ratio of 0.70. Full details about the futility analysis decision rules and procedures will be specified in an IDMC charter, which will also specify the roles and responsibility of the IDMC members. Conducting the futility analysis results in power loss, but no alpha adjustment is required as there is no decision rule in place for stopping the study early to claim efficacy and no recovery of alpha from the futility analysis.

A data cut off for an interim analysis to inform sponsor Phase 3 planning will be conducted 1 month after Last Subject Randomised. The study will continue, even if sufficient efficacy is observed to inform an early go for planning purposes. The IDMC will be used and a blinding plan will be written to ensure that the study team, investigational site staff and subjects remain blinded to subject level treatment revealing data if an early planning decision is made. As the study will continue regardless, no adjustment to the type I error, alpha, is required.

6. CHANGE OF ANALYSIS FROM PROTOCOL

There are no changes of analysis from the protocol.

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8. APPENDIX

8.1 Adverse events of special interest

8.1.1 Serious hypersensitivity reactions

Serious hypersensitivity reactions are defined as a combination of anaphylactic reactions (used with a time restriction) and events meeting regulatory serious criteria within the 'Hypersensitivity' narrow SMQ (no time restriction).

A subject will be considered to have this AESI if the subject has at least one adverse event with onset date during the relevant study period for analysis, which satisfies either of the following:

8.1.1.1 Anaphylactic reactions

- Potential anaphylactic reactions will be defined on the basis of Sampson's criteria (see Sampson et al., 2006). These will be identified using a modified Standardised MedDRA Query (SMQ), with additional constraints on the timing of the AE onset date relative to the timing of the injection.

- Confirmed anaphylactic reactions will be those defined following medical review of the preferred terms identified as potential anaphylactic reactions, as well as any relevant supporting data.

8.1.1.2 Hypersensitivity

- Events meeting regulatory serious criteria within the 'Hypersensitivity' narrow SMQ.

AESIs and related definitions based on MedDRA terms are not included in this SAP to facilitate their maintenance (e.g. management of MedDRA version changes), and for convenience in using them directly in SAS programming. These detailed definitions will be finalised by the study team prior to primary DBL of the trial, and provided together with the study datasets at the time of submission.

8.1.2 Malignancy

Malignancy will be defined on the basis of an SMQ, using "SMQ: Malignant or unspecified tumors".

AESIs and related definitions based on MedDRA terms are not included in this SAP to facilitate their maintenance (e.g. management of MedDRA version changes), and for convenience in using them directly in SAS programming. These detailed definitions will be finalised by the study team prior to primary DBL of the trial and provided together with the study datasets at the time of submission.

8.1.3 Helminth infections

Helminth infection will use an investigator-driven definition, i.e. will be directly determined from what is entered on the eCRF.

A subject will be considered to have this AESI if the subject has at least one preferred term where the dedicated Helminth Infection eCRF page was also completed for that event (linked by AE number), with AE onset date during the relevant study period for analysis.

8.1.4 Serious infections

Serious infections are defined as events meeting regulatory serious criteria within the 'Infections and infestations' SOC.

8.1.5 Guillain-Barre syndrome

Guillain-Barre syndrome will be defined using an SMQ.

AESIs and related definitions based on MedDRA terms are not included in this SAP to facilitate their maintenance (e.g. management of MedDRA version changes), and for convenience in using them directly in SAS programming. These detailed definitions will be finalised by the study team prior to primary DBL of the trial and provided together with the study datasets at the time of submission.

8.1.6 Serious cardiac events

Serious cardiac events are defined as events meeting regulatory serious criteria within the 'Cardiac disorders' SOC.

8.2 Accounting for missing data

Accounting for missing data for recurrent events (moderate/severe COPD exacerbation rate endpoint, severe COPD exacerbation rate endpoint)

In this study some subjects dropping out of the study potentially leads to unobserved events. The amount of missing data is minimised in this study as subjects are allowed in the protocol to switch to an alternative treatment or treatments after they discontinue from randomised treatment and are encouraged to complete visits until they withdraw from the study.

This section summarises how we will describe the pattern of and reasons for missing data from the study. It will also describe how we plan to account for missing data, including both the primary and

sensitivity analyses to assess the robustness of the treatment effect under different underlying assumptions to account for missing data.

Missing data descriptions

Tabular summaries for the percentage of subjects by the reason for discontinuation of randomised treatment as well as for withdrawal from the study will be presented by treatment group to describe why subjects discontinue from randomised treatment or withdraw from the study. The time to discontinuation of randomised treatment and withdrawal from the study will be presented using Kaplan Meier plots (overall and split by treatment related/not treatment related reason for withdrawal / IP discontinuation, as defined in Table 4 and Table 5respectively). Dependent on these outputs additional exploratory analyses may be produced as deemed necessary to further understand the pattern of missing data.

Primary analysis under the primary estimand using the missing at random (MAR) assumption

The primary analysis for the primary endpoint of moderate to very severe COPD exacerbations allows for differences in outcomes over the study treatment period up to 52 weeks to reflect the effect of initially assigned randomised treatment as well as if subsequent treatments are taken. This primary analysis utilises all data over the 52-week period regardless of whether subjects remain on randomised treatment or whether they use an alternative biologic treatment. The primary analysis uses the negative binomial regression model with (logarithm of) the time at risk as an offset term and assumes that missing data are missing at random (MAR) and is a direct likelihood approach (DL).

Sensitivity analyses under the primary estimand using both MAR and missing not at random (MNAR) assumptions

To examine the sensitivity of the results of the primary analysis to departures from the underlying assumptions, additional analyses will be performed using controlled multiple imputation method introduced in [1] and further developed at AstraZeneca [2,3] which allows for different underlying assumptions to be used. As with the primary analysis, the sensitivity analyses include all data over the 52-week period regardless of whether subjects remain on randomised treatment or use an alternative biologic treatment.

For this method an underlying negative binomial stochastic process for the rate of exacerbations is assumed and post study withdrawal counts will be imputed conditional upon the observed number of events prior to the withdrawal. This allows various assumptions about the missing data to be analysed by modifying the post-withdrawal model assumption.

The method involves first fitting the primary analysis, i.e., negative binomial regression model to the observed data and then imputing post-withdrawal counts by sampling from the conditional negative binomial probability relating post-withdrawal counts and observed prior-withdrawal counts based on various assumptions.

$$\Pr\left(Y_{ij,2} = y_2 \middle| Y_{ij,1} = y_1\right) = \frac{\Gamma(\gamma + y_1 + y_2)}{\Gamma(y_2+1)\Gamma(\gamma + y_1)} p_j^{y_2}(1-p_j)^{\gamma + y_1} \qquad (1)$$

Here y_1 is number of counts before withdrawal from the study, y_2 is number of counts after withdrawal from the study, γ is the dispersion parameter and which is assumed to be the same for different treatment arms, *j* denotes the treatment arm and *i* denotes the subject identifier. Furthermore

$$p_j = \frac{p_{j,2} - p_{j,1}p_{j,2}}{1 - p_{j,1}p_{j,2}} \qquad (2)$$

where $p_{j,1}$ is the negative binomial distribution (NBD) rate parameter before withdrawal from the study, and $p_{j,2}$ is the rate parameter after withdrawal from the study as determined based on various assumptions.

The imputed number of exacerbations that would have been seen is then combined with the observed exacerbations and data is analysed using the primary analysis methodology (DL). This analysis is repeated multiple times and the results combined using Rubin's formulae [7, 8].

The following default assumptions that may be used to impute the missing data for subjects who withdraw early from the study are as follows:

a) MAR: Missing counts in each arm are imputed assuming the expected event rate within that arm.

b) Dropout Reason-based Multiple Imputation (DRMI): Missing counts will be imputed differently depending on the reason for dropout; counts for subjects in the tezepelumab treatment arm who dropped out for a treatment related reason are imputed based on the expected event rate in placebo, whereas the remaining subjects who have dropped out are imputed assuming MAR. Treatment related reasons include (1) AEs, (2) Death and (3) development of study specified reasons to stop active treatments.

Some reasons for withdrawal are clearer to determine as treatment related (*Adverse Events, Death, Development of study-specific discontinuation criteria*) or non-treatment related (*Subject lost to follow up, eligibility criteria not fulfilled*). Other reasons are less clear such as site or study terminated by sponsor, subject decision and 'Other'; a review of each subject who withdraws from the study will therefore be carried out prior to unblinding the study. The review will include assessment of the reason for discontinuation of randomised treatment for those subjects who discontinued randomised treatment and then withdrew from the study and also free text for when the reason for withdrawal or discontinuation of randomised treatment is recorded as subject decision or other. Based on this review the default assumptions for DRMI as described in b) and Table 4 may be changed. A list of these subjects and the assumptions made under DRMI will be documented prior to unblinding of the study.

A summary of reasons for subjects withdrawing from the study and the corresponding arm used to calculate the imputed exacerbation rate under MAR and MNAR (DRMI) is given in Table 4.

Table 4 Reason for withdrawal

Reason for withdrawal	MAR	DRMI
Adverse Event	Tezepelumab	Placebo
Development of study-specific withdrawal criteria*	Tezepelumab	Placebo
Death	Tezepelumab	Placebo
Subject lost to follow up	Tezepelumab	Tezepelumab
Subject decision	Tezepelumab	Based on review prior to study unblinding
Site terminated by sponsor	Tezepelumab	Based on review prior to study unblinding
Study terminated by sponsor	Tezepelumab	Based on review prior to study unblinding
Physician decision	Tezepelumab	Based on review prior to study unblinding
Failure to meet randomisation criteria	Tezepelumab	Based on review prior to study unblinding
Other	Tezepelumab	Based on review prior to study unblinding

Note exacerbation rates for subjects in the placebo arm are imputed using the placebo arm rate
*Development of study-specific discontinuation criteria are based on the following: anaphylactic reaction to the IP requiring administration of epinephrine, development of helminth parasitic infestations requiring hospitalisation, a COPD-related event requiring mechanical ventilation; intensive care unit admission with intubation or extensive mechanical ventilation for a COPD related event

Together with the primary analysis, the sensitivity analyses are considered to cover the range from realistic to plausible worst-case assumptions about missing data. The MAR multiple imputation approach is expected to correspond closely to the primary analysis and is included to allow for comparisons with MNAR assumptions (specifically method b) using the same multiple imputation methodology.

The dropout reason-based multiple imputation (DRMI) approach was selected as the most conservative approach based on the fact that placebo subjects are receiving standard of care and are not expected to change to a substantially more effective treatment after withdrawing from study or study treatment. For subjects receiving tezepelumab who withdraw from the study due to treatment related reasons it is

assumed that at worst they would be on the standard of care treatment, i.e., the placebo arm. For subjects receiving tezepelumab who withdraw from the study due to non-treatment related reasons it seems reasonable to assume they would be similar to those subjects who complete treatment.

Sensitivity analysis under the supplemental estimand

The sensitivity analysis under the primary estimand using both MAR and MNAR (as described above) may be repeated under the supplemental estimand, where all available data will be included over the 52-weeks period until subjects discontinue randomised treatment or begin treatment with alternative biologic therapy, if the Kaplan-Meier plot split by treatment related/not treatment related reasons for IP discontinuation suggests any interesting patterns.

Imputation of missing counts up to Week 52 (including study withdrawal) will be performed for the primary endpoint of moderate or severe COPD exacerbations and for the severe COPD exacerbations endpoint as described above. For subjects who begin treatment with an alternative biologic therapy, data will be imputed by assuming subjects received tezepelumab. For those who discontinue randomised treatment (and do not start on alternative biologic therapy) the appropriate treatment arm used to calculate the imputed exacerbation rate under MAR and DRMI are given in Table 5. As for subjects who withdraw from the study, a review of each subject who discontinued randomised treatment will be carried out prior to unblinding the study where the default assumptions for DRMI as described in Table 5 may be changed. Again, a list of these subjects and the assumptions made under DRMI will be documented prior to unblinding of the study.

Table 5 Reason for discontinuation of randomised treatment

Reason for discontinuation of randomised treatment	MAR	DRMI
Adverse Event	Tezepelumab	Placebo
Development of study-specific discontinuation criteria*	Tezepelumab	Placebo
Severe non-compliance to protocol	Tezepelumab	Placebo
Subject lost to follow up	Tezepelumab	Tezepelumab
Subject decision	Tezepelumab	Based on review prior to study unblinding
Other	Tezepelumab	Based on review prior to study unblinding

Note exacerbation rates for subjects in the placebo arm are imputed using the placebo arm rate
*Development of study-specific discontinuation criteria are based on the following: anaphylactic reaction to the IP requiring administration of epinephrine, development of helminth parasitic infestations requiring hospitalisation, a COPD-related event

requiring mechanical ventilation; intense care unit admission with intubation or extensive mechanical ventilation for a COPD related event

Overall summary of analyses to account for missing data

A summary of the analyses to be carried out under different missing data assumptions are described in **Error! Reference source not found.**.

Table 6 Summary of analyses

Assumption	Primary and supplemental estimands		
		MAR	**MNAR**
	DL	**MAR**	**DRMI**
Exacerbation rate for imputation in Teze arm[b]	No explicit imputation[a]	Teze for all reasons for withdrawal	Placebo for AEs, Death, and development of study specified discontinuation criteria, otherwise Teze or based on review prior to study unblinding.
Default definition for $\boldsymbol{p_{j,1}}$ and $\boldsymbol{p_{j,2}}$ based on formula (2)[c].		$p_{j,2} = p_{j,1}$ For all treatment arms j=T and P	$p_{\mathrm{T},2} = p_{\mathrm{P},1}$ $p_{\mathrm{P},2} = p_{\mathrm{P},1}$ for reasons above otherwise $p_{\mathrm{T},2} = p_{T,1}$

[a] Implicitly assumes unobserved rate the same as observed
[b] Exacerbation rates for all subjects in the placebo arm are imputed using the placebo arm rate (i.e., $\mathrm{p_{P,2}} = \mathrm{p_{P,1}}$)
[c] Note can be over written by review prior to study unblinding

T Tezepelumab 420 mg; P Placebo

Forest plots will be used to show the primary analysis results along with the missing data sensitivity analysis results. The rate ratio of tezepelumab versus placebo and corresponding 90% CI will be displayed in the x-axis.

It is noted that if the primary analysis is statistically significant, it is not necessarily expected that all sensitivity analyses will also give statistically significant results. If the results of the sensitivity analyses provide reasonably similar estimates of the treatment effect to the primary analysis, this will be interpreted as providing assurance that neither the lost information nor the mechanisms which cause the data to be missing have an important effect on primary analysis conclusions. Based on these outputs and the drug's mechanism of action, the plausibility of the assumptions we make about missing data in the different analyses will be considered and described in the clinical study report.

Accounting for missing data for continuous endpoints (FEV_1 and SGRQ total score)

Primary analysis using the MAR assumption

As for the primary variable, the primary analysis of the FEV_1 and SGRQ total score as secondary endpoints will handle intercurrent events as per the primary estimand. The MMRM used is a DL approach in each case, which is valid under the MAR assumption.

Sensitivity analysis using MNAR assumptions

Sensitivity analyses of the repeated measures analyses will be performed for the FEV_1 and SGRQ total score using controlled sequential multiple imputation methods based on pattern mixture models as described in [5].

The method is analogous to the multiple imputation of exacerbation events and the imputation process consists of a sequence of MI steps, where each step is intended to impute missing values at 1 time-point only. This model will assume that some pre-specified subset of subjects who withdraw from the study have correlations with future (unobserved) visits similar to subjects in the placebo arm. As for the exacerbation events, this allows us to assess various deviations from the MAR assumption.

The assumptions that will be used to impute the missing data who withdraw early are as follows:

(a) MAR: Assumes that the trajectory for subjects who dropped out in each arm is similar to those observed in their own treatment arm

(b) DRMI: Assumes that the trajectory for subjects in the tezepelumab treatment arm who dropped out for treatment related reasons (according to the same classification as for the DRMI analysis of the primary endpoint) is similar to that of the placebo subjects, whereas the remaining subjects who has dropped out are imputed assuming MAR.

Approach b) can be considered more conservative than the approach for the primary analysis because the assumptions mean that as soon as subjects withdraw for a treatment related reason, they begin to worsen immediately.

The MNAR imputation is achieved by only using appropriate data at each stage of the imputation. Imputation will be done in 2 steps, the non-monotone (intermediate) missing SGRQ total score and FEV_1 values will be imputed first [Markov chain Monte Carlo (MCMC) method is used to partially impute the data using SAS PROC MI] and then the missing value at each visit will be imputed using a sequential regression method (using MONOTONE REG option of SAS PROC MI).

For example, to impute missing values at time t for subjects in the tezepelumab treatment arm, that dropped out due to an AE, include only placebo observations up to and including time t, plus observations from subjects in the tezepelumab arm that dropped out due to an AE, up to and including time t-1. This is done for each visit, one at a time using observed data, and missings just imputed.

Placebo missing observations and tezepelumab observations that are not missing due to AEs are imputed assuming missing at random (MAR) and follow the pattern of observed placebo observations in each treatment arm respectively. 100 imputations will be carried out, and a seed of 407016 will be used for the monotone imputation step and a seed of 766275 will be used for the sequential regression imputation step. The analysis of each of the imputed datasets will be as described for the primary analysis in Section 4.2.5.5 and Section 4.2.5.6 and these will be combined using SAS procedure PROC MIANALYZE.

To avoid possible convergence issues when fitting MMRM models to 100 imputed datasets, the estimated unstructured covariance parameters from the first imputation where the model converges will be used as the starting values to fit the models for all imputed datasets.

Results for continuous endpoints will be presented as per the recurrent event sensitivity analyses.

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8.3 Efficacy estimands

Statistical category	Estimand			SAP Section
	Endpoint (Population)	**Intercurrent event strategy**	**Population level summary (Analysis)**	
Primary objective: To evaluate the effect of tezepelumab 420 mg as compared with placebo on COPD exacerbations in subjects with moderate to very severe COPD				
Primary	•Annual rate of moderate/severe COPD exacerbations up to Week 52 (FAS)	• Included regardless of whether subjects remain on randomised treatment (primary estimand) • Included until subjects discontinue randomised treatment or begin treatment with alternative biologic therapy (supplemental estimand)	Rate ratio for interventions (NB model)	4.2.4.1
Sensitivity	•Annual rate of moderate/severe COPD exacerbations up to Week 52 (FAS)	• Withdrawal from study (primary estimand) assumed to be MAR • Withdrawal from study (primary estimand) assumed to be MNAR	• Rate ratio for interventions (NB model with MI from same randomised arm off-treatment) • Rate ratio for interventions (NB model with drop-out reason-based MI)	Appendix 8.2
Supportive to primary	•Annual rate of moderate or severe COPD exacerbations up to Week 52 (FAS) excluding exacerbations treated only with antibiotics	• Included regardless of whether subjects remain on randomised treatment (primary estimand)	Rate ratio for interventions (NB model)	4.2.4.1
Secondary Objective: To evaluate the effect of tezepelumab 420 mg as compared to placebo on severe COPD exacerbations				
Secondary	•Annual rate of severe COPD exacerbations up to Week 52 (FAS)	•Included regardless of whether subjects remain on randomised treatment (as per primary estimand)	Rate ratio for interventions (NB model)	4.2.5.3

Statistical category	Estimand			SAP Section
	Endpoint (Population)	**Intercurrent event strategy**	**Population level summary (Analysis)**	
Sensitivity	•Annual rate of severe COPD exacerbations up to Week 52 (FAS)	• Withdrawal from study (as per primary estimand) assumed to be MAR • Withdrawal from study (as per primary estimand) assumed to be MNAR	• Rate ratio for interventions (NB model with MI from same randomised arm off-treatment) • Rate ratio for interventions (NB model with drop-out reason-based MI)	Appendix 8.2
Secondary Objective: To evaluate the effect of tezepelumab 420 mg as compared with placebo on pre-bronchodilator (BD) lung function				
Secondary	•CFB in pre-BD FEV_1 at Week 52 (FAS)	• Included regardless of whether subjects remain on randomised treatment (as per primary estimand) • Included until subjects discontinue randomised treatment or begin treatment with alternative biologic therapy (as per supplemental estimand)	Mean difference between interventions (LSMD in CFB MMRM (by visit))	4.2.5.5
Sensitivity	• CFB in pre-BD FEV_1 at Week 52 (FAS)	• Withdrawal from study (as per primary estimand) assumed to be MAR • Withdrawal from study (as per primary estimand) assumed to be MNAR	• Mean difference between interventions (LSMD in CFB MMRM with MI from same randomised arm off-treatment) • Mean difference between interventions (LSMD in CFB MMRM with drop-out reason-based MI)	Appendix 8.2
Secondary Objective: To evaluate the effect of tezepelumab 420 mg as compared with placebo on respiratory health status/health-related quality of life				
Secondary	• CFB in SGRQ total score at Week 52 (FAS)	• Included regardless of whether subjects remain on randomised treatment (as per primary estimand) • Included until subjects discontinue randomised treatment or begin treatment with alternative biologic therapy (as per supplemental estimand)	Mean difference between interventions (LSMD in CFB MMRM (by visit))	4.2.5.6
Sensitivity	• CFB in SGRQ total score at Week 52 (FAS)	• Withdrawal from study (as per primary estimand) assumed to be MAR	• Mean difference between interventions (LSMD in CFB MMRM with MI from same randomised arm off-treatment)	Appendix 8.2

Statistical category	Estimand			SAP Section
	Endpoint (Population)	**Intercurrent event strategy**	**Population level summary (Analysis)**	
		• Withdrawal from study (as per primary estimand) assumed to be MNAR	• Mean difference between interventions (LSMD in CFB MMRM with drop-out reason-based MI)	
Secondary	• Proportion of SGRQ responders at Week 52 (FAS)	• Included regardless of whether subjects remain on randomised treatment (as per primary estimand)	• Odds ratio of interventions (logistic regression)	4.2.5.7
Sensitivity	• Proportion of SGRQ responders at Week 52 (FAS)	• Included regardless of whether subjects remain on randomised treatment (as per primary estimand)	• Odds ratio of interventions (logistic regression using LOCF imputation)	4.2.5.7

EOT = End of treatment; IPD = Investigational product discontinuation. NB = Negative binomial; MI = Multiple imputation; MAR = Missing at random; DRMI = Drop-out reason-based multiple imputation; LSMD = Least squares mean difference; CFB = Change from baseline; MMRM = Mixed model for repeated measures; BD = Bronchodilator; SGRQ = St. George's Respiratory Questionnaire; FAS = Full Analysis Set; LOCF = Last observation carried forward.

8.4 Additional reporting to assess the impact of the COVID-19 pandemic

Additional summaries will be produced, and analyses carried out, to assess the impact of the COVID-19 pandemic on study results. The summaries and analyses are detailed below, referencing the section of the SAP to which they relate.

COVID-19 phases (pre- / during- / post-)

The start of the COVID-19 pandemic will be defined as 11th March 2020 (the date the WHO declared COVID-19 to be a pandemic).

The end of the COVID-19 pandemic will be defined as 5th May 2023 (the date the WHO declared COVID-19 is no longer constitutes a public health emergency of international concern).

Data recorded before the start date will be *pre-pandemic*; data recorded on or after the end date will be *post-pandemic.* All data recorded on or after the start date and before the end date will be *during-pandemic*.

Violations and deviations (SAP Section 2.2)

All COVID-related IPDs will be summarised (as per Section 4.2.1) and listed, together with all non-COVID-related IPDs. A separate listing will be produced of all COVID-19-related protocol deviations (important and non-important) by treatment group. An additional summary will present IPDs related to COVID-19 and IPDs excluding those related to COVID-19 separately, by treatment group, for the FAS.

COVID-19-related study disruptions

A COVID-19-related study disruption is *any* change in the study conduct, or the data collected due to the COVID-19 pandemic. Examples of COVID-19-related study disruptions include:

- Changes to visit schedules, missed visits, changes to study procedures;
- Discontinuation of IP or changes to the IP supply.

An additional table – COVID-19-related study disruptions - will summarise all disruptions for the FAS. The number and percentage of subjects randomised pre-pandemic will be reported along with the number and percentage of subjects ongoing during the pandemic. If applicable, the number and percentage of subjects randomised post-pandemic will be reported.

The number and percentage of subjects with at least one COVID-19-related study disruption will be reported. Total pre-pandemic, during-pandemic and, if applicable, post-pandemic follow-up

times will be presented in total subject years and also as proportions of total follow-up time (in years), as an indication of the proportion of study time potentially affected by COVID-19.

The number and percentage of subjects who missed at least one IP dose, the number and percentage missing 1, 2, 3, 4 and 5+ doses and the number and percentage of subjects with 2, 3, 4, 5, and more than 5 consecutive missed doses due to COVID-19 will be presented.

The number and percentage of subjects with at least one missed scheduled visit, or changed format of scheduled visit, will be summarised by treatment group. Impacted visits will be classified as "Fully completed", Partially completed", "Delayed" or "Not done". Reasons for impact will be classified as "Subject decision due to pandemic concerns", "Pandemic related logistic issues" and "Other". Visits fully or partially completed will be further classified by contact mode as "Remote – audio", "Remote – video", "On-site" and "Other".

A listing of all subjects impacted by COVID-19 will be produced with details of changed or missed visits and changed or missed IP administration due to COVID-19.

Analysis of primary outcome variable (SAP Section 4.2.4.1)

An additional analysis of the primary endpoint will be carried out to compare exacerbation rates in the tezepelumab group with those in the placebo group during the pre-pandemic phase. The analysis will use pre-pandemic observed data only, i.e. data over the 52-week exacerbation follow-up period up to and including 10th March 2020 only. The comparison will otherwise be under the primary estimand, using all observed data in this period regardless of adherence to randomised treatment or the use of an alternative biologic treatment**.**

Annualised exacerbation rates in the tezepelumab group will be compared to annualised exacerbation rates in the placebo group using a negative binomial model. The response variable will be the number of COPD exacerbations experienced by a subject during the follow-up for exacerbations (see Section 3.2.1.1) prior to 11th March 2020. The model will include covariates of treatment group, region, and the number of exacerbations in the year prior to study entry (2, ≥3). The logarithm of the subject's corresponding time at risk (see Section 3.2.1.1) prior to 11th March 2020 will be used as an offset variable in the model. Marginal standardisation methods will be used and results will be presented as for the primary analysis.

Two additional sensitivity analyses will compare annualised exacerbation rates in the tezepelumab group with those in the placebo group using during-pandemic/post-pandemic data only. The first will use all observed data from 11th March 2020 until the earlier of: the end of the exacerbation follow-up period (see Section 3.2.1.1); or the day prior to the end of the pandemic. The second will use all observed data from 5th May 2023 until the earlier of: the end of the exacerbation follow-up period. The analyses will otherwise be under the primary estimand (i.e. including all relevant data regardless of adherence to randomised treatment or the use of an alternative biologic treatment).

Analysis of secondary outcome variables

Time to first COPD exacerbation (SAP Section 4.2.5.1)

An additional analysis of the time to first exacerbation will be carried out using pre-pandemic data only. The analysis will include all available data over the 52-week exacerbation follow-up period up to and including 10th March 2020. For subjects who do not experience a COPD exacerbation prior to 11th March 2020, the time to first COPD exacerbation will be censored at 10th March 2020 (if prior to the end of the maximum follow-up time as described in Section 3.2.1.1). A Cox proportional hazard model will be fitted to the data as described in Section 4.2.5.1.

Adverse Events (SAP Section 4.2.7.1)

All AE-related analyses described below will be based on the safety analysis set using the on-treatment period.

The overall AE summary table (AEs in any category reported) will be repeated by pandemic phase: pre-pandemic, during-pandemic and post-pandemic (if applicable). Categories will include: any AEs, SAEs, AEs with a fatal outcome, DAEs, COVID-19 AEs (as defined based on MedDRA version 23.1 (September 2020) terms) and non-COVID-19 related AEs.

Summary statistics of AEs and SAEs by SOC and PT using exposure adjusted incidence rates will be provided by pandemic phase: pre-pandemic, during-pandemic and post-pandemic (if applicable). Summary statistics for COVID-19 AEs and non-COVID-related AEs by SOC and PT using exposure adjusted incidence rates will be provided for the during-pandemic phase.

In addition, if there are more than 10 subjects reporting COVID-19 AEs, then the AE listing will be repeated including only these subjects, with details of all AEs reported by these subjects.

A listing of subjects tested for COVID-19 will be provided, with all available test data and results. The listing will include: type of test (PCR /serology); date of test; associated visit number; time on-treatment (if applicable); and test result.

For the adjudication AE summary tables, the number of subjects reporting AEs that were adjudicated to be related to COVID-19 will be included. The adjudication listing will show the adjudicated relationship to COVID-19 (related, not related, undetermined, and not applicable). Not applicable will be used for AEs with an onset date prior to 01 January 2020.

8.5 Handling incomplete dates for adverse events and medications

8.5.1 Partial dates for adverse events and prior/concomitant medication

Dates missing the day or both the day and month of the year will adhere to the following conventions to classify AEs and to classify prior/concomitant medications.

8.5.1.1 Partial dates for adverse events

Onset date of AEs

If only the day of the AE onset date is missing, the missing day will be set to:

- First day of the month that the event occurred, if the onset YYYY-MM is after the YYYY-MM of first study treatment
- The day of the first study treatment, if the onset YYYY-MM is the same as YYYY-MM of the first study treatment
- The date of informed consent, if the onset YYYY-MM is before the YYYY-MM of the first treatment

If both of the day and month of the onset date of an AE are missing, the onset date will be set to:

- January 1 of the year of onset, if the onset year is after the year of the first study treatment.
- The date of the first treatment, if the onset year is the same as the year of the first study treatment
- The date of informed consent, if the onset year is before the year of the first treatment

Resolution date of AEs

If only the day of the AE resolution date is missing, the missing day will be set to:

- The last day of the month of the occurrence. If the patient died in the same month, then set the imputed date as the death date

If both of the day and month of the resolution date of an AE are missing, the date will be set to:

- December 31 of the year of occurrence. If the patient died in the same year, then set the imputed date as the death date

8.5.1.2 Partial dates for prior/concomitant medication

Start date of prior/concomitant medication

- If only the day is missing, then the start date of a therapy will be set to the first day of the month that the event occurred
- If both the day and month are missing, then the start date of a therapy will be set to January 1 of the year of onset
- If the start date of a therapy is completely missing then the date will be set as following.
  - If the end date is not a complete date then the start date will be set to the date of the first study visit

- If the end date is a complete date,
  - And the end date is after the date of the first study visit then the start date will be set to the date of the first study visit
  - Otherwise, the start date will be set to the end date of the therapy

End date of prior/concomitant medication

- If only the day is missing, then the end date of a therapy will be set to the last day of the month of the occurrence
- If both the day and month are missing, then the end date of a therapy will be set to December 31 of the year of occurrence
- If the end date of a therapy is completely missing then the date will be set as following
  - If the start date is not a complete date then the end date will be set to the date of the last study visit
  - If the start date is a complete date
    - And the start date is prior to the date of the last study visit then the end date will be set to the date of the last study visit

Otherwise, the end date will be set to the start date of the therapy