Cover page

Document title: A Multicenter, Single-arm, Open-label, Post-Authorization, Phase 4 Effectiveness and Safety Study of Tezepelumab in Adult and Adolescent Participants with Severe Asthma including Several Under-Studied Populations in the United States (PASSAGE)

Version number: 3.0

Date of the document: 11 June 2025

STATISTICAL ANALYSIS PLAN	
Study Code	D5180C00032
Edition Number	3.0
Date	11-Jun-2025

A Multicenter, Single-arm, Open-label, Post-Authorization, Phase 4 Effectiveness and Safety Study of Tezepelumab in Adult and Adolescent Participants with Severe Asthma including Several Under-Studied Populations in the United States (PASSAGE)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AAER	Annualized Asthma Exacerbation Rate
ACQ	Asthma Control Questionnaire
AE	Adverse event
AESI	Adverse event of special interest
AIRQ	Asthma Impairment and Risk Questionnaire
APAS	All Participants Analysis Set
CGI-C	Clinical Global Impression of Change
CRF	Case Report Form
COPD	Chronic obstructive pulmonary disease
CSP	Clinical Study Protocol
CRSwNP	Chronic rhinosinusitis with nasal polyps
CRSsNP	Chronic rhinosinusitis without nasal polyps
DAE	Adverse event leading to discontinuation of tezepelumab
ECG	Electrocardiogram
ED	Emergency department
FAS	Full Analysis Set
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced expiratory volume in 1 second
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICE	Intercurrent event
Ig	Immunoglobulin
ICS	Inhales corticosteroids
IPD	Important Protocol Deviation
LSMD	Least Squares Mean Difference
MCID	Minimum clinically important difference
OCS	Oral corticosteroids
PD	Protocol Deviation
PGIC	Patient's Global Impression of Change
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCS	Systemic corticosteroids

Abbreviation or Specialized Term	Definition
SGRQ	St. George's Respiratory Questionnaire
SNOT	Sino-nasal Outcome Test
SMQ	Standardized MedDRA Query
TA	Therapeutic Area
TNSS	Total Nasal Symptom Score
TSQM	Treatment Satisfaction Questionnaire from Medication
UC	Urgent care

AMENDMENT HISTORY

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
N/A	14-Apr-2022	Initially Approved SAP	Yes (v2)	Initial SAP. In line with CSP version 2.0 (24 Jan 2022).
Other	04-May-2023	Section 2: - Stated that FPC is a binary endpoint and will be analysed with appropriate methodology; the next version of the CSP will be updated to reflect this change. - Included detail about the removal of the TNSS responder analysis	N/A	To provide additional clarity
Other	14-Mar-2023	Section 3.1: Updated language about timing of interim analyses to be more flexible.	Yes (v3)	To align with CSP v3
Other	14-Mar-2023	Section 3.3.1.1: Moved the on-treatment period section (formerly Section 3.3.1.4) to Section 3.3.1.1 to keep all definitions together.	N/A	To provide additional clarity
Other	14-Mar-2023	Sections 3.3.1.2 and 3.3.1.5: Removed these sections as their contents have been added to more applicable sections	N/A	To remove redundancies
Other	14-Mar-2023	Section 3.3.1.2: Added wording that unscheduled/repeat assessments can be	N/A	To provide additional clarity

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
		considered for baseline assessments given they occur before the first dose of study intervention.		
Data presentations	14-Mar-2023	Section 3.3.1.4 (formerly 3.3.1.6): - Added wording about regional perennial panels to subgroups #2 and #12 - Added Baseline BEC <150 cells/microliter to subgroup definition #11 for completeness	N/A	To provide additional clarity
Other	14-Mar-2023	Section 3.3.1.6 (formerly 3.3.1.8): Added clarifying details to the Asthma exacerbation definition	Yes (v3)	To align with CSP v3
Other	14-Mar-2023	Section3.3.1.6(formerly 3.3.1.8): Moved the Time to first asthma exacerbation definition to Section 4.2.2	N/A	To provide additional clarity
Other	14-Mar-2023	Section 3.3.1.7 (formerly 3.3.1.9): Changed the name of 'relative change' to 'percent change'	N/A	To align with development program
Data presentations	14-Mar-2023	Section 3.3.2: Added detail regarding - the calculation of relative day - how to address unscheduled or repeat visits	N/A	To provide additional clarity

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
		- how to deal with multiple assessments recorded on the same day - difference between 4-weekly visit windows and sparse visit windows Updated Table 2 with all visit windows (4-weekly visits and sparse visits) to avoid gaps in data collection.		
Data presentations	14-Mar-2023	Section 3.3.3: Clarified that data collected at unscheduled or repeat visits will also be windowed and may be included in summaries	N/A	To align with development program
Data presentations	14-Mar-2023	Section 4.1.1.2: - Removed the summary of number of participants that are ongoing on treatment and in study - Added summary of participants who discontinued treatment but completed the study	N/A	To align with development program and reduce redundancy in displays
Data presentations	14-Mar-2023	Section 4.1.2.2: Added that protocol deviations related to the global/country situation will be summarised	N/A	To align with development program
Data presentations	14-Mar-2023	Section 4.1.4:	N/A	To align with development program

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
		- Removed disease characteristics from this section and added it to its own section - Added baseline characteristics to be summarised		
Data presentations	14-Mar-2023	Section 4.1.5: Added new section for disease characteristics separate from baseline characteristics (Section 4.1.4).	N/A	To align with development program
Other	14-Mar-2023	Section 4.1.7.1(formerly 4.1.6.1): Added definitions for prior, concomitant, on-treatment, and off-treatment medications	N/A	To provide additional clarity
Data presentations	14-Mar-2023	Section 4.1.7.2 (formerly 4.1.6.2): Specified that outputs for prior, concomitant (on-treatment), and concomitant (post-treatment) will be produced	N/A	To align with development program
Data presentations	14-Mar-2023	Section 4.1.8.2 (formerly 4.1.7.2): Added that the number of study intervention administrations impacted by the global/country situation will also be summarised	N/A	To align with development program
Data presentations	14-Mar-2023	Section 4.2: Table 3 updated endpoint wording	Yes (v3)	To align with CSP v3
Other	14-Mar-2023	Section 4.2.1.2:	N/A	To provide additional clarity

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
		- Added details for derivations of time at risk - Moved reduction in exacerbations, percent reduction, and responder analyses to the supportive analysis section as they are not primary analyses		
Statistical analyses	14-Mar-2023	Section 4.2.1.4: - Updated the statistical model for the primary endpoint to be a GEE model instead of a linear model - Clarified that Subject will be included in the model using the REPEATED statement	N/A	To align with analysis method
Other	14-Mar-2023	Section 4.2.1.6: Added text that was formerly in primary analysis section to this section	N/A	To provide additional clarity
Other	14-Mar-2023	Section 4.2.1.7: Added that the AAER will also be summarised by the type and number of asthma triggers (formerly this analysis was stated in its own section)	N/A	To provide additional clarity
Data presentations	14-Mar-2023	Section 4.2.2: Time to first asthma exacerbation endpoint was added	Yes (v3)	To align with CSP v3

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
Other	04-May-2023	Section 4.2.5.2 Changed relative to percent for change from baselines	N/A	To provide additional clarity
Other	04-May-2023	Section 4.2.8 (formerly 4.2.6): - Specified that only SCS for asthma will be summarised - Added detail for the derivation of cumulative SCS dose and cumulative annualized SCS dose	N/A	To provide additional clarity
Data presentations	04-May-2023	Section 4.2.13 (formerly 4.2.10): Clarified that FPC is a binary endpoint (not continuous) and added detail for appropriate analysis method	N/A	To align with analysis method
Other	04-May-2023	Section 4.2.19 (formerly 4.2.14): - Added detail that clinical remission will be evaluated at both Visit 8 and Visit 15 - Stated that remission will only be evaluated for those who complete Visit 8 or Visit 15, respectively - Clarified how patients who are and are not on OCS at baseline will be categorized - Updated ACQ-6 cut off from 0.75 to 1.5	N/A	To provide additional clarity and align with development program

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
Data presentations	04-May-2023	Section 4.2.6.1: Updated AESIs	Yes (v3)	To align with CSP v3
Data presentations	04-May-2023	Section 4.2.6.1: Added that exposure adjusted incidence rates will also be calculated and summarised	N/A	To align with development program
Data presentations	04-May-2023	Section 4.2.6.2: - Added that SAEs with an outcome of death will be summarised by SOC and PT - Added COVID-19 summaries - Added key subject information summaries	N/A	To align with development program
Other	04-May-2023	Throughout Section 4.2: - Removed text relating to the ICE strategy from all applicable 'Handling of Dropouts and Missing Data' sections as this is not true data imputation - Stated that no data imputation will be performed - Text relating to outcome definitions that was previously listed under 'Derivations' was moved to the appropriate 'Definition' sections	N/A	To provide additional clarity

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
		- Endured that all endpoints had their own Section		
Other	14-Mar-2023	Section 5: Updated language about timing of interim analyses to be more flexible.	Yes (v3)	To align with CSP v3
Other	04-May-2023	Appendix 7.1: Simplified AESI information	Yes (v3)	To align with CSP v3 and development program
Other	04-May-2023	Throughout: - Updated all instances of 'IP' to 'study intervention' - Updated all instance of 'ER' to 'ED/UC'	Yes (v3)	To align with CSP v3
Other	18 July 2024	Clinical remission – updated criteria for defining clinical remission, to remove footnote 'a', which states "In order to give the study intervention time to work exacerbations that occur during the first 4 weeks after the initiation of tezepelumab will not be included in the analysis."	N/A	To align with development program
Other	18 July 2024	Updated relative day definition for assessments that occur before the index date.	N/A	To provide additional clarity
Other	18 July 2024	Updated baseline definition for safety output.	N/A	To provide additional clarity

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
Other	18 July 2024	Updated primary analysis of SNOT-22 to include the model for repeated measures.	N/A	To align with analysis method
Other	18 July 2024	Additional subgroup added for asthma exacerbations: Baseline exacerbations [≥2 exacerbations]. Added subgroup analysis for pre-BD and post-BD FEV1: Baseline pre-BD FEV1 (% predicted) ≤ 80%, Phase 1 and Phase 2 subgroups, Baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 1 subgroups, and Baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 2 subgroups. Added subgroup analysis for ACQ-6: Baseline ACQ-6 ≥ 1.5, Phase 1 and Phase 2 subgroups, ACQ-6 ≥ 1.5 among Phase 1 groups, ACQ-6 ≥ 1.5 among Phase 2 subgroups, Baseline ACQ-6 ≥ 1.5 and Visit 15 ACQ-6 ≥ 1.5, Baseline ACQ-6 ≥ 1.5 and Visit 15 ACQ-6 < 1.5, Baseline ACQ-6 ≥ 1.5 and Visit 8 ACQ-6 <1.5 and Visit 1.5 ACQ-6 < 1.5.	N/A	To align with development program

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
		Added subgroup analysis for AIRQ: Baseline AIRQ ≥ 2; Phase 1 and Phase 2 subgroups, Baseline AIRQ ≥ 2 among Phase 1 subgroups, and Baseline AIRQ ≥ 2 among Phase 2 subgroups. Added subgroup analysis for SGRQ, SCS use, TSQM and CGI-C score, post-BD FEV1, asthma trigger analysis and clinical remission: Phase 1 and Phase 2 subgroups. Added subgroup analysis for adherence/persistence, duration of therapy, discontinuation, and reasons for discontinuation after initiation of tezepelumab: Phase 1 and Phase 2 subgroups. Added subgroup analysis for frequent productive cough (FPC) composite score: Among participants with baseline FPC; Severe asthma without COPD and		

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
		baseline FPC, Mild and Moderate COPD and baseline FPC. Added subgroup analysis for Patient's Global Impression of Change (PGIC) score for COPD: Comorbid COPD, comorbid mild COPD, comorbid moderate COPD. Added subgroup analysis for TNSS score: Among participants with baseline symptoms, Allergic rhinitis and baseline symptoms; CRS (wNP or sNP) and baseline symptoms, CRSwNP and baseline symptoms and CRSsNP and baseline symptoms. Added subgroup analysis for SNOT-22 total score: CRS (CRSwNP and CRSsNP), CRSwNP; CRSsNP, CRSwNP with prior surgical history, and CRSwNP without prior surgical history.		
Other	5 September 2024	Added subgroup analysis for pre-BD FEV1, ACQ-6, AIRQ and SGRQ:	N/A	To align with development program

Category: Change refers to	Date	Description of Change	In line with the CSP?	Rationale
		Baseline number of asthma trigger: ≥ 4; Baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Baseline number of asthma trigger: ≥ 4.		
Statistical analysis	12 May 2025	Updated the Cumulative SCS primary analysis to include a mixed model and summarised categories		To align with development program
Statistical analysis	12 May 2025	Updated the derivation of asthma-related HRU annual rates and primary analysis of the HRU endpoint		To align with development program

1 INTRODUCTION

This statistical analysis plan (SAP) provides a detailed description of the methodology for the statistical analyses to support the final clinical study report (CSR) for Protocol D5180C00032 (PASSAGE). The SAP is based on the following study documents: PASSAGE CSP version 3.0 (Amendment 2), 12 Jan 2023 and the eCRF version 6.0, 19 Feb 2025 (RR5). All references to study protocol or eCRF hereafter refer to these versions.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

CSP v3.0 states that the frequent productive cough (FPC) endpoint is continuous and be analysed using change from baseline methodology. FPC is a binary endpoint and will be analysed using appropriate categorical statistical methods.

CSP v3.0 includes an endpoint for the proportion of TNSS responders defined as participants who achieve ≥1 MCID. The TNSS version being used in this study differs from the traditional twice daily assessment that is typically implemented. As such, an appropriate MCID cannot be identified and therefore responders cannot be defined. In the absence of an identifiable threshold, the TNSS responder analysis has been removed from this version of the SAP.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The final analysis will be performed after all participants have completed all visits and the database has been locked. It includes all tables, listings and figures specified in the latest version of the TFL shell document and will be used to write the CSR.

3.2 Analysis Populations

The following populations will be defined:

3.2.1 All Participants Analysis Set (APAS)

The APAS comprises all participants screened for the study and will be used for reporting of disposition and screening failures.

3.2.2 Full Analysis Set (FAS)

The FAS includes all enrolled participants who received at least one dose of tezepelumab, irrespective of their protocol adherence and continued participation in the study. Participants will be analysed irrespective of whether they prematurely discontinue, according to the intent-to-treat principle. Participants who withdraw from the study or die will be included up to the date of their study termination/death. All safety and efficacy

analyses will be performed using the FAS. For consistency, demographics and baseline characteristics will be presented using the FAS.

3.3 General Considerations

3.3.1 General Study Level Definitions

3.3.1.1 Study Periods

The following study periods will be used to report the results of the study. All refer to the Index date (Week 0; Visit 1 or 2), which is the date when a participant received the first tezepelumab dose.

- **Baseline Period (Week -52 to Week 0):** The Baseline Period is defined as the 12-months prior to the index date (Week 0). The start date of the Baseline Period is calculated as *(index date – 365 days)*. The end date of the Baseline Period is calculated as *(index date – 1)*.
- **On-treatment Period**: The Treatment Period starts on the index date and ends on earliest date of last dose of study intervention + 35 days, date of death, or date of study withdrawal. The date of study withdrawal is the completion or discontinuation date from the Disposition eCRF page, where any participant status other than "Completed" has been entered.
- **Study Period (Week 0 to Week 52):** The Study Period consists of the Treatment Period (Week 0 to Week 48) and the Follow-up Period (Week 48 to 52). It starts on the index date and ends on the study completion or withdrawal date.

3.3.1.2 Baseline

For asthma exacerbations, baseline is the 12-months (52 weeks) prior to the index date (Week 0) also known as the 12-month baseline period before initiation of tezepelumab.

For other efficacy outputs, assessments done at the last non-missing measurement prior to or on first dose of tezepelumab will serve as the baseline measurement. If there is no value prior to first dose of tezepelumab, then the baseline value will not be imputed, and will be set to missing.

Where unscheduled/repeated assessments exist for any participant at a particular visit, they are also considered in the baseline definitions, provided they remain prior to the date of first dose of study intervention.

For safety outputs, the last non-missing measurement prior to the first dose of tezepelumab (including date and time) will serve as the baseline value.

3.3.1.3 Imputation of Missing Dates

For the analyses of on-treatment AEs and concomitant medications, a complete start date needs to be reported in the eCRF. In case of completely missing dates or incomplete dates that make it impossible to determine if the medication was concomitant or an adverse event was on-treatment, it will be assumed that medication is concomitant, or an adverse event is on-treatment. The same will apply for dates of asthma exacerbations and HRU. If it is not possible to determine if the asthma exacerbation or HRU occurs prior or post first dose of study drug because of completely or partially missing dates, it will be assigned to be in the Study Period. Partial and completely missing start and end dates will be imputed as described below.

Imputation of missing start dates

- If only the month and year are specified and the month and year of first dose of tezepelumab is not the same as the month and year of the start date, then use the 1st of the month,
- if only the month and year are specified and the month and year of first dose of tezepelumab is the same as the month and year of the start date, then use the date of first dose of tezepelumab,
- if only the year is specified, and the year of first dose of tezepelumab is not the same as the year of the start date, then use the 1-January of the year of the start date,
- if only the year is specified, and the year of first dose of tezepelumab is the same as the year of the start date, then use the date of first dose,
- if the start date is completely unknown and the end date is unknown OR not prior to the date of first dose of tezepelumab, then use the date of first dose of tezepelumab,
- if the imputed start date is after the known end date, set the start date to be the same as the end date.

Imputation of missing end dates

- If only the month and year are specified and the month and year are the same as the study end date, then use the day of the study end date,
- if only the month and the year are specified and the month and year are not the same as the study end date, then use the last day of the month,
- if only the year is specified and the year is the same as the year of the study end date, then use the day and month of the study end date,
- if only the year is specified and the year is not the same as the year of the study end date, then use 31-December of that year,
- if the end date is completely unknown, then use the last available date in the study (Visit 15, Early Termination Visit, death, lost to follow up).

3.3.1.4 Subgroups

By study design participants are enrolled in a two-target approach in order to describe effectiveness of tezepelumab in a broad population of patients across traditional asthma phenotypes of high (≥300) and low (<300) BEC (per uL) and allergic status and for several under-represented populations of interest. For the statistical analysis there will be a set of subgroups defined as priority subgroups for which a minimum number of participants to analyse is defined by study design. In addition, a set of exploratory subgroups will be defined for exploratory analyses and will be used for statistical analysis if the sample size will permit. Permissible sample size is at least 10 participants per subgroup for the primary objective analysis (Section 4.2.1).

The following subgroups are defined as priority subgroups and include participants with:

1. Baseline BEC (uL) [<300, ≥300 cells/microliter],
    a. Baseline BEC classification for all subgroup classification in Section 3.3.1.4 is based on the highest documented BEC during the 12-month baseline period, excluding counts within 0-30 days following systemic corticosteroid (SCS) use.
2. Baseline perennial specific IgE (kU/L) status (FEIA) [Any perennial FEIA positive, All perennial FEIA negative]:
    a. "Any perennial FEIA positive" requires 1 or more of the panel specific IgE (kU/L) (FEIA) tests to be "Positive". Provided at least one panel FEIA test is "Positive", no further requirement is made for data on the remaining panel perennial FEIA tests to be available.
    b. All perennial FEIA negative" requires all panel perennial FEIA tests to be negative (some tests results may be missing or unknown).

Note that "Positive" is defined as a value ≥0.35 kU/L. More information regarding the FEIA panels is included in Section 3.3.1.5.

3. Phase 1 subgroups: Baseline BEC [<300, ≥300 cells/microliter] and baseline perennial specific IgE (kU/L) status (FEIA) [Any perennial FEIA positive, All perennial FEIA negative]:
    a. Baseline BEC <300 cells/microliter and with any perennial FEIA positive,
    b. Baseline BEC ≥300 cells/microliter and with any perennial FEIA positive,
    c. Baseline BEC <300 cells/microliter and with all perennial FEIA negative,
    d. Baseline BEC ≥300 cells/microliter and with all perennial FEIA negative.

See subgroup definition #2 above for definitions of "Any perennial FEIA positive" and "All perennial FEIA negative".

4. Phase 2 subgroup: Race [Black or African American],
5. Phase 2 subgroup: Age group [12 ≤ age < 18 years (adolescents)],
6. Phase 2 subgroup: Baseline comorbid COPD status [mild to moderate (GOLD 2021)],
7. Phase 2 subgroup: Baseline smoking status [≥10 pack-years of smoking],
8. Baseline CRSwNP status [Yes]: Defined by the presence of the following on the Respiratory Medical History eCRF: ongoing nasal polyps,
9. Baseline exacerbations [≥2 exacerbations],
10. Baseline number of patient-reported asthma triggers: ≥ 4.

Exploratory subgroups will include the following:

11. Baseline BEC [<150, ≥150, 150-<300, 300-<450, ≥450 cells/microliter],
12. Baseline BEC [<150, ≥150, 150-<300, 300-<450, ≥450 cells/microliter] and baseline perennial specific IgE (kU/L) status (FEIA) [Any perennial FEIA positive, All perennial FEIA negative]:
    a. Baseline BEC <150 cells/microliter and with any perennial FEIA positive,
    b. Baseline BEC ≥150 cells/microliter and with any perennial FEIA positive,
    c. Baseline BEC ≥150 and <300 cells/microliter and with any perennial FEIA positive,
    d. Baseline BEC ≥300 and <450 cells/microliter and with any perennial FEIA positive,
    e. Baseline BEC ≥450 cells/microliter and with any perennial FEIA positive,
    f. Baseline BEC <150 cells/microliter and with all perennial FEIA negative,
    g. Baseline BEC ≥150 cells/microliter and with all perennial FEIA negative,
    h. Baseline BEC ≥150 and <300 cells/microliter and with all perennial FEIA negative,
    i. Baseline BEC ≥300 and <450 cells/microliter and with all perennial FEIA negative,
    j. Baseline BEC ≥450 cells/microliter and with all perennial FEIA negative.
13. Clinically-relevant allergy to a perennial aeroallergen [evidence of clinically-relevant perennial allergy, lack of evidence of clinically-relevant perennial allergy]:
    a. "evidence of clinically-relevant perennial allergy" requires 1 or more perennial allergy pairs to be positive. Provided that at least one perennial allergy pair is "Positive", no further requirement is made for data on all other perennial allergy pairs to be available,

b. "lack of evidence of clinically-relevant perennial allergy" requires all tested perennial allergy pairs to be "Negative" (some tests might be missing or unknown).

Clinically-relevant allergy to a perennial aeroallergen is defined as a clinical history of asthma symptoms driven by exposure to a perennial aeroallergen and sensitization to the corresponding perennial aeroallergen(s) based on a positive result to serum allergen-specific immunoglobulin (IgE) (kU/L) testing.

Further details of this subgroup derivation, including definition of perennial allergy pairs, are defined separately in Section 3.3.1.5.

14. Baseline BEC [<150, ≥150, 150-<300, 300-<450, ≥450 cells/microliter] and clinically-relevant allergy to a perennial aeroallergen [evidence of clinically-relevant perennial allergy, lack of evidence of clinically-relevant perennial allergy]:
    a. Baseline BEC <150 cells/microliter and with evidence of clinically-relevant perennial allergy,
    b. Baseline BEC ≥150 cells/microliter and with evidence of clinically-relevant perennial allergy,
    c. Baseline BEC ≥150 and <300 cells/microliter and with evidence of clinically-relevant perennial allergy,
    d. Baseline BEC ≥300 and <450 cells/microliter and with evidence of clinically-relevant perennial allergy,
    e. Baseline BEC ≥450 cells/microliter and with evidence of clinically-relevant perennial allergy,
    f. Baseline BEC <150 cells/microliter and with lack of evidence of clinically-relevant perennial allergy,
    g. Baseline BEC ≥150 cells/microliter and with lack of evidence of clinically-relevant perennial allergy,
    h. Baseline BEC ≥150 and <300 cells/microliter and with lack of evidence of clinically-relevant perennial allergy,
    i. Baseline BEC ≥300 and <450 cells/microliter and with lack of evidence of clinically-relevant perennial allergy,
    j. Baseline BEC ≥450 cells/microliter and with lack of evidence of clinically-relevant perennial allergy.
15. Baseline regional seasonal specific IgE (kU/L) status (FEIA) [Any regional seasonal FEIA positive, All regional seasonal FEIA negative]:

a. "Any regional seasonal FEIA positive" requires 1 or more of the regional panel specific IgE (kU/L) (FEIA) tests to be "Positive". Provided at least one regional panel FEIA test is "Positive", no further requirement is made for data on the remaining regional panel perennial FEIA tests to be available.
b. "All regional seasonal FEIA negative" requires all regional panel seasonal FEIA tests to be negative (some tests results may be missing or unknown).

Note that "Positive" is defined as a value ≥0.35 kU/L. More information regarding the regional FEIA panels is included in Section 3.3.1.5.

16. Clinically-relevant allergy to a regional seasonal aeroallergen [evidence of clinically-relevant regional seasonal allergy, lack of evidence of clinically-relevant regional seasonal allergy]:
    a. "evidence of clinically-relevant regional seasonal allergy" requires 1 or more regional seasonal allergy pairs to be positive. Provided that at least one regional seasonal allergy pair is "Positive", no further requirement is made for data on all other regional seasonal allergy pairs to be available,
    b. "lack of evidence of clinically-relevant regional seasonal allergy" requires all tested regional seasonal allergy pairs to be "Negative" (some tests might be missing or unknown).

Clinically-relevant allergy to a regional seasonal aeroallergen is defined as a clinical history of asthma symptoms driven by exposure to a regional seasonal aeroallergen and sensitization to the corresponding seasonal aeroallergen(s) based on a positive result to serum allergen-specific immunoglobulin (IgE) (kU/L) testing.

Further details of this subgroup derivation, including definition of regional seasonal allergy pairs, are defined separately in Section 3.3.1.5.

17. Baseline FeNO [<25, 25-<50, ≥50 ppb],
18. Age at onset of asthma [<18, ≥18, ≥18 to <40, ≥40 years],
19. Asthma duration [<20 and ≥20 years],
20. Baseline ongoing diagnosis of allergic rhinitis [Yes],
21. Baseline ongoing diagnosis of atopic dermatitis [Yes],
22. BMI category (see Section 4.1.4.1)
23. Baseline predicted pre-BD FEV1 [<80% and ≥80%],
24. Ethnicity [Hispanic or Latino],

25. Baseline CRSsNP [Yes]

    Chronic rhinitis/sinusitis without nasal polyps at baseline will be defined by the presence of the following on the Respiratory Medical History eCRF for a particular subject: No history of nasal polyps and at least one ongoing diagnosis of rhinitis or chronic sinusitis.

26. Baseline smoking status [current, former, never],
27. Baseline smoking status [current or former with <10 pack years, current or former with ≥ 10 pack years],
28. Baseline patient-reported asthma triggers by the following categories:
    a. Infections [Viral infection and other infections],
    b. Allergens [Year-round allergies, seasonal allergies, and dust],
    c. Environmental [Exercise/physical activity, weather changes, air pollution, smoke, strong smells or fumes, and cleaning/housework],
    d. Others [All other (Strong emotions, acid reflux, specific foods, changes in asthma medications, specific medication not for asthma)].
29. History of biologic for asthma use for the treatment of asthma [with history of biologic for asthma use, or without history of biologic for asthma use]. The biologics are reslizumab, mepolizumab, benralizumab, omalizumab, and dupliumab.
30. Sensitization to each individual aeroallergen (across all reported perennial and seasonal aeroallergens),
31. Clinically-relevant allergy based on individual aeroallergen sensitization (across all reported perennial and seasonal aeroallergens),
32. Asthma triggers categories:
    a. Allergen,
    b. Aspirin,
    c. Exercise,
    d. Other,
33. Other comorbid ongoing diagnoses.

Any history of medication will be collected on the Prior and Concomitant Medication eCRF. Prior Systemic Corticosteroids (mg) are collected on the Systemic Corticosteroids (ECSYSCRT) eCRF. The definition of prior medication can be found in Section 4.1.7.1.

3.3.1.5 Clinically-relevant Allergy To An Aeroallergen

As defined in CSP Amendment 3, clinically-relevant allergy is defined as a clinical history of asthma symptoms driven by exposure to an aeroallergen and the sensitization to the

corresponding aeroallergen(s) based on a positive result to serum allergen-specific IgE (kU/L) testing by Fluorescent Enzyme Immunoassay (FEIA) at baseline.

To achieve this, serum allergen-specific IgE (kU/L) test by FEIA (further on: FEIA test) collected in the LB1 eCRF will be matched with corresponding historical allergy agent(s) collected in the ALLERH eCRF. Note that a specific FEIA test may be matched with more than one historical allergy agent, e.g. Immunoglobulin E, Cat Dander Allergen FEIA test from the LB1 eCRF is matched with both Cat and Animals Unspecified historical allergy agents from the ALLERH eCRF.

Thus, for each FEIA test, a following allergy pair will be derived: (sensitization component, history component), where

- Sensitization component: a FEIA test,
- History component: a list of one or more matching historical allergy agents.

A pair will be categorized as "Positive", if both components are "Positive". If at least one component is "Negative", the pair is considered "Negative". The list of all possible specific allergy pairs is provided in Table 1 (note that not all seasonal allergy pairs will be tested in every region).

Sensitization component is defined as "Positive" if the specific IgE (kU/L) test value is ≥ 0.35 kU/L, or "Negative" if the specific IgE (kU/L) test value is < 0.35 kU/L.

History component is categorized as "Positive" if at least one of the allergy agents were confirmed in the data collected in the ALLERH eCRF. If none of the agents were confirmed, history component is considered "Negative".

Table 1 All possible specific allergy pairs

Pair no	FEIA test	Seasonal or Perennial	Historical allergy agents
1	Alternaria mold	Perennial	Microfungi unspecified or Alternaria
2	Aspergillus fumigatus	Perennial	Microfungi unspecified
3	Aspergillus niger	Perennial	Microfungi unspecified
4	Cladosporium	Perennial	Microfungi unspecified or Cladosporium or Hormodendrum
5	Penicllium notatum	Perennial	Microfungi unspecified or Penicillum
6	Cat dander	Perennial	Cat or Animals Unspecified
7	Dog dander	Perennial	Dog or Animals Unspecified
8	Mouse urine	Perennial	Mouse or Animals Unspecified
9	D. Farinae	Perennial	D. Farinae or House dust unspecified
10	D. Pteronyssinus	Perennial	D. Pteronyssinus or House dust unspecified

Pair no	FEIA test	Seasonal or Perennial	Historical allergy agents
11	House dust	Perennial	D. Pteronyssinus, D. Farinae, or House dust unspecified
12	German cockroach	Perennial	Cockroach or Animals Unspecified
13	American cockroach	Perennial	Cockroach or Animals Unspecified
14	Oriental cockroach	Perennial	Cockroach or Animals Unspecified
15	American Elm or White Elm	Seasonal	Ulmus Americana or Trees Unspecified
16	Grey Alder	Seasonal	Alder Alnus Incana or Trees Unspecified
17	Birch	Seasonal	Betula Verrucoca or Trees Unspecified
18	Silver Birch	Seasonal	Common Silver Birch or Trees Unspecified
19	Sycamore/Maple	Seasonal	Acer and/or Platanus Species or Trees Unspecified
20	Sycamore	Seasonal	Sycamore (Platanus) or Trees Unspecified
21	Pecan Tree	Seasonal	Carya Pecan or Trees Unspecified
22	Walnut	Seasonal	Juglans Species or Trees Unspecified
23	Black Walnut	Seasonal	Juglnas Nigra or Trees Unspecified
24	Oak	Seasonal	Quercus Species or Trees Unspecified
25	White Oak	Seasonal	Quercus Alba or Trees Unspecified
26	Elm	Seasonal	Ulmus Species or Trees Unspecified
27	Cottonwood	Seasonal	Populus Species or Trees Unspecified
28	Eastern Cottonwood	Seasonal	Populus Deltoides or Trees Unspecified
29	Arizona Cottonwood	Seasonal	Populus Fremontii or Trees Unspecified
30	White Ash	Seasonal	Fraxinus Americana or Trees Unspecified
31	Olive Tree	Seasonal	Olea Europaea or Trees Unspecified
32	Maple Box Elder	Seasonal	Maple Box Elder or Trees Unspecified
33	White Mulberry	Seasonal	Morus Alba or Trees Unspecified
34	Mountain Juniper	Seasonal	Juniperus Sabinoides or Trees Unspecified
35	Japanese Cedar	Seasonal	Japanese Cedar Tree or Trees Unspecified
36	Mountain Cedar	Seasonal	Mountain Cedar Jun Protein or Trees Unspecified
37	Timothy Grass	Seasonal	Timothy Grass
38	Bermuda Grass Pollen	Seasonal	Cynodon Dactylon
39	Bahia Grass	Seasonal	Bahia Grass
40	Johnson Grass	Seasonal	Johnson Grass
41	Kentucky Blue Grass	Seasonal	Kentucky Blue Grass
42	Common Ragweed	Seasonal	Common Ragweed or Weeds Unspecified
43	Short Ragweed	Seasonal	Common Short Ragweed or Weeds Unspecified
44	Common Pigweed or Rough Pigweed	Seasonal	Amaranthus Retroflexus or Weeds Unspecified

Pair no	FEIA test	Seasonal or Perennial	Historical allergy agents
45	Sagebrush Mugwort	Seasonal	Artemisia Vulgaris or Weeds Unspecified
46	Rough Marsh Elder	Seasonal	Rough Marsh Elder or Weeds Unspecified
47	Common Sheep Sorrel	Seasonal	Rumus Acetosella or Weeds Unspecified
48	Prickly Saltwort or Russian Thistle	Seasonal	Salsola Kali or Weeds Unspecified

Note: Tested seasonal allergens are regionally dependent.

3.3.1.6 Asthma Exacerbation

Asthma exacerbations will be defined by worsening of asthma symptoms that leads to any of the following:

- a temporary bolus/burst of systemic corticosteroids (SCSs) (mg) or a temporary increase in stable OCS background dose for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of SCSs,
- an emergency room (ED)/ or urgent care (UC) visit (defined as evaluation and treatment for <24 hours in an ED/UC center) due to asthma that required SCS (as per above),
- an inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma.

The Investigator must justify the decision for defining an event of worsening asthma as an exacerbation.

The start of an exacerbation is defined in the CSP as the start date of SCS, ED/UC visits requiring SCS, or hospital admissions due to asthma, whichever occurs earlier. The end date is defined in the CSP as the last day of SCS or ED/UC/hospital discharge, whichever occurs later.

Additional SCS, ED visits requiring use of SCS, or inpatient hospitalisation due to asthma will not be counted as a new exacerbation if the end date of the first exacerbation and the start date of the second exacerbation are less than 7 days apart.

3.3.1.7 Change From Baseline

Change from baseline will be of interest for various assessments performed during this study. If either the post-baseline value or the baseline value is missing, then the respective change from baseline will also be missing.

The absolute change from baseline is defined for the assessments of interest as

(post-baseline value – baseline value).

The percent change from baseline in % is defined as

(Absolute change from baseline / baseline value) ×100%.

Unless specified otherwise, "change from baseline" is assumed to be the absolute change from baseline. Baseline calculations are defined in Section 3.3.1.2.

3.3.2 Visit Window

All summaries and analyses, which are presented by time point will use a visit window to classify the study assessments. The relative day will be used for assessing if the visit is scheduled in the visit window. This allows appropriate classification of visits which may have occurred significantly earlier or later than the protocol assessment schedule.

The relative day will be calculated as *(Date of assessment – Date of first dose of study intervention) + 1* for assessments that occur after the index date. For assessments that occur before the index date the following formula will be used: *(Date of assessment – Date of first dose of study intervention)*.

Data collected at unscheduled or repeated visits are also included in visit windows and therefore may be included in summaries or analyses by visit. 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 replaces the missing value at the scheduled visit.

Each assessment that will fall into a visit window of a specific visit will be linked to this visit. If more than one assessment is available in a specific visit window, the one closest to the target day will be selected for analysis. If two assessments are recorded on the same day and have a different assessment time associated with both, the assessment with the earliest time will be selected for analysis. If two assessments (for continuous variables) 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, the average of the two values are selected for analysis at that visit. For categorical variables in this situation, the worst case is used, which is taking the assessment closest to the index date.

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

Visit windows for each study visit are shown in Table 2. "4-weekly Visit Window" corresponds to the 4-weekly protocol scheduling for clinic visits, including those variables which are not captured at every clinic visit, unless otherwise stated.

Sparse visit windows are defined also for specific parameters not measured every 4 weeks. There are three different groups that fall under the "Sparse Visit Window" depending on when parameters were collected:

- Group 1: Parameters collected at Visit 2, Visit 8, and Visit 15 (Lung function test, ACQ-6, AIRQ, SGRQ, TNSS, and SNOT-22),
- Group 2: Parameters collected at Visit 8 and Visit 15 only (TSQM-9, CGI-C, and PGI-C),
- Group 3: Parameters collected at Visit 2 and Visit 15 only (Asthma trigger survey, BEC, Total IgE, and specific IgE).

Table 2 Visit windows for all study visits

Visit (Time Point)	Target Day	4-weekly Visit Window (Days)	Sparse Visit Window (Sparse CSP schedule)		
			Group 1	Group 2	Group 3
Visit 2 (Day 1)	1	See Section 3.3.1.2 for baseline definitions			
Visit 3 (Week 4)	29	2-42	-	-	-
Visit 4 (Week 8)	57	43-70	-	-	-
Visit 5 (Week 12)	85	71-98	-	-	-
Visit 6 (Week 16)	113	99-126	-	-	-
Visit 7 (Week 20)	141	127-154	-	-	-
Visit 8 (Week 24)	169	155-182	141-198	141-198	-
Visit 9 (Week 28)	197	183-210	-	-	-
Visit 10 (Week 32)	225	211-238	-	-	-
Visit 11 (Week 36)	253	239-266	-	-	-
Visit 12 (Week 40)	281	267-294	-	-	-
Visit 13 (Week 44)	309	295-322	-	-	-
Visit 14 (Week 48)	337	323-350	-	-	-
Visit 15 (Week 52)	365	351-378	337-378	337-378	337-378

In all cases above, no time points are presented in summary tables or included in statistical analysis which do not correspond to the time points scheduled in the protocol for the variable in question.

3.3.3 Handling of Unscheduled Visits

Data collected at unscheduled or repeat visits are also included in visit windows and therefore may be included in summaries or analyses by visit. For the analyses displayed according to study visit, please refer to Section 3.3.2 to determine scheduled/unscheduled visit handling.

3.3.4 Multiplicity/Multiple Comparisons

No formal hypothesis will be tested in this study, and therefore no multiplicity adjustment will be applied in the statistical analysis.

3.3.5 Analysis Sets

3.3.5.1 Definitions and Derivations

3.3.5.2 Presentation

The number of participants in the APAS and FAS will be summarized. Participants excluded from the FAS will be listed.

3.3.6 Handling of Protocol Deviations in Study Analysis

Important protocol deviations (IPD) are those deviations from the protocol identified by the study team as important and requiring summary in the CSR. The criteria for identifying important protocol deviations will be defined within the Protocol Deviation Plan. Protocol deviations will be reviewed periodically through the study as part of the ongoing data cleaning process and the important deviations are identified and documented and integrated into the clinical database.

IPDs are defined as PDs which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a participant's rights, safety or well-being. Important PDs in this study will be grouped under one of the following categories:

- did not fulfil key eligibility criteria,
- informed consent was not provided,
- study intervention administration deviations,
- did not adhere to protocol-required procedure and visit window.

IPDs will not be used to exclude any participant from any analysis set, nor to exclude any data from participants included in any analysis set.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

In general, continuous variables will be summarized using the mean, standard deviation, median, minimum value, and maximum value, and categorical variables will be summarised using frequency counts and percentages. Minimum and maximum value will be reported to the same number of decimal places as the raw data recorded in the database. All other statistics (mean, median, SD, CIs) will have one additional decimal place more than the raw data recorded in the database.

Statistical analyses for this study will be conducted using SAS® v9.4 or latest version in a secure and validated platform.

Data will be listed in participant-level data listings by timepoint if specified per objective (Section 4.2).

4.1 Study Population

The domain study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant medication and study drug compliance.

4.1.1 Participants' Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Study withdrawal

A participant will be defined as withdrawn from the study if the participant status on the "Disposition" eCRF is other than "Completed" and there is a discontinuation date entered.

Study completers

Participants who completed the study will have the participant status "Completed" in the "Disposition" eCRF page. A participant can be a study completer despite discontinuing study intervention prematurely.

Premature discontinuation of treatment

Participants who discontinue treatment prematurely will have a "study intervention discontinuation date" in the "Discontinuation of Study Intervention" eCRF specified.

4.1.1.2 Presentation

Disposition will be summarized for the APAS.

Disposition includes number and percentages (if applicable) of

- participants screened,

- screen failures and reasons for screen failures (after first and second rescreening),
- participants started, completed or discontinued treatment prematurely including the reason for discontinuation of treatment and option selected by a subject after study intervention discontinuation (as per CSP Section 7.1),
- participants completed study,
- participants who discontinued treatment but completed the study,
- participants withdrawn from study including the reason for withdrawal.

4.1.2 Protocol Deviations

4.1.2.1 Definitions and Derivations

The definition of important protocol deviations and the grouping in categories can be found in section 3.3.6.

4.1.2.2 Presentation

The number and percentage of participants with any IPD and the number and percentage of participants in the IPD categories will be summarized and listed for the FAS.

Information of participants with important protocol deviation is also listed.

PDs related to global/country situation are defined in the Protocol Deviation Plan. The IPD related to global/country situation are summarised together with all other Important PDs as described in section 3.3.6. An additional summary is provided of Important PDs related to global/country situation and Important PDs excluding global/country situation related Important PDs for the FAS.

4.1.3 Demographics

4.1.3.1 Definition and Derivations

For the presentations defined in this section, age group will be categorized as follows:

- ≥12 – < 18 years,
- ≥18 – <65 years,
- ≥ 65 years.

Age is derived from the *date of informed consent – date of birth*, rounded to the nearest integer.

4.1.3.2 Presentation

Demographics will include

- age,
- age group (see Section 4.1.3.1),
- sex,
- race (Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, White, Other, multiple, Not reported),
- ethnicity (Hispanic or Latino, Not Hispanic or Latino).

Demographics will be summarized and listed for the FAS.

4.1.4 Baseline Characteristics

4.1.4.1 Definitions and Derivations

For the presentations defined in this section, BMI group will be categorised as follows:

- <25 (kg/m^2),
- ≥25- <30 (kg/m^2),
- ≥30 (kg/m^2),
- ≥30- <35 (kg/m^2),
- ≥35 (kg/m^2)

4.1.4.2 Presentation

Baseline characteristics will be summarized by FAS and include:

- Weight (kg) and height (cm),
- BMI (kg/m^2),
- BMI category (see Section 4.1.4.1),
- pre-BD FEV1,
- pre-BD FEV1 (% Predicted),
- number and percentage of pre-BD FEV1 (% predicted) ≤ 80%,
- Daily SCS dose,
- Biomarker levels (FeNO (ppb), BEC (1/uL), and IgE (kU/L)),
- Biomarker level categories (see Section 3.3.1.4),
- Clinically relevant allergic status (see definitions #11 and #14 in Section 3.3.1.4),
- number and percentage of current, former and never smokers,
- total number of pack years for cigarettes.

These variables will be collected for the Baseline Period. For the definition of Baseline Period see Section 3.3.1.1.

4.1.5 Disease Characteristics

4.1.5.1 Definitions and Derivations

Asthma and COPD diagnosis date will be collected in the eCRF. The duration of asthma and COPD will be derived from the date of first diagnosis relative to the index date.

Age at onset of asthma = Asthma diagnosis year – Year of birth + 1.

Age at onset of COPD = COPD diagnosis year – Year of birth + 1.

4.1.5.2 Presentation

Baseline asthma and COPD characteristics will be summarised for the FAS and include:

- number and percentage of participants with asthma diagnosis by the GINA classification,
- number and percentage of participants by asthma triggers,
- asthma duration (years),
- age at onset of asthma (years),
- number and percentage of participants with COPD diagnosis by the GOLD classification (GOLD 2021),
- COPD duration (years)
- number and percentage of participants with prior history of chronic rhinosinusitis with nasal polyps,
- number and percentage of participants with prior nasal polyp surgery,
- number and percentage of participants with ongoing diagnosis of chronic rhinosinusitis with nasal polyps,
- number and percentage of participants with ongoing diagnosis of chronic rhinosinusitis without nasal polyps,
- number and percentage of participants with ongoing diagnosis allergic rhinitis,
- number and percentage of participants with ongoing diagnosis atopic dermatitis,
- number of non-biologic asthma medications (ICS, asthma maintenance controller),
- number and percentage of participants with prior biologic asthma medication.

4.1.6 Medical History

Medical history excluding asthma related conditions and respiratory medical history will be summarized separately for the FAS. Respiratory medical history terms will be reported by

the categories listed in the Respiratory Medical History eCRF. Medical history will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT).

Respiratory medical and medical history will be listed including start and end dates and the information if the condition is ongoing at the time of enrolment.

4.1.7 Prior and Concomitant Medications

4.1.7.1 Definitions and Derivations

Medications taken by any participant at any time during the study will be coded using the ATC classification system within the WHO Drug Dictionary. Medication will be categorized by being administered together with the study drug (concomitant medication) or being stopped before the start of study treatment (prior medication).

Prior medication – defined as those medications stopped before first dose of study intervention:

- end date of medication ≤ date of first dose of study intervention.

Concomitant medication – defined as those medications either started or continued after the first dose of study intervention. Concomitant medications are also defined on-treatment and off-treatment period as follows:

On-treatment period concomitant medication:

- medication end date ≥ date of first dose of study intervention and medication start date ≤ earliest (date of last dose of study intervention + 35 days; date of death, date of study withdrawal) or
- medication end date ongoing and medication start date ≤ earliest (date of last dose of study intervention + 35 days, date of death, date of study withdrawal).

Post-treatment period concomitant medication:

- medication start date > date of last dose of study intervention + 35 days.

If a medication started and stopped at the date of first dose of study intervention, it is considered concomitant.

The handling of partial/missing dates for prior/concomitant medications is detailed in Section 3.3.1.3.

4.1.7.2 Presentation

The number and percentage of participants receiving each medication by ATC classification system codes and generic names will be presented for the FAS. Separate

tables are presented for all medications received during each of the following periods: prior, concomitant (on-treatment), concomitant (post-treatment) as defined in Section 4.1.7.1. Similar tables are presented for subjects who took disallowed concomitant medications.

The number and percentage of participants receiving systemic corticosteroids (mg) during the on-treatment period is summarised by route of administration.

Prior and concomitant medications will be listed including start and end dates, route of administration, total daily dose, frequency, indication and therapy reason for each participant in the FAS. Percentages are calculated relative to the number of participants in the FAS.

4.1.8 Study Drug Compliance

4.1.8.1 Definitions and Derivations

Study drug compliance will be calculated as follows:

Study drug compliance (%) = [(Total number of actual dosing occasions/total number of expected dosing occasions) x *100%].*

In order to allow for participants who prematurely discontinue tezepelumab 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 participant. The maximal number of expected dosing will be 13 for participants who did not discontinue treatment prematurely and did not miss any dose.

4.1.8.2 Presentation

Compliance and total number of dosing occasions to study drug will be summarized and listed for the FAS.

The number of participants with study intervention administration impacted by global/country situation, including consecutive missed doses, is summarised. In addition, the number of study intervention doses administered by location (home, other) is summarised.

4.2 Endpoint Analyses

This section covers details related to primary, secondary and exploratory endpoints including sensitivity and supportive analyses. All analyses will be done using the FAS. All variables shown in summaries will also be listed.

Data after the initiation of another biologic that impacts asthma control will be excluded from the efficacy analyses unless specified otherwise.

The FAS will be used for all of the analyses specified below:

Table 3 Overview Objectives

Statistical category	Endpoint	Subgroups to analyze	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To describe asthma exacerbations in the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period)					
Primary	Annualized asthma exacerbation rate (AAER) over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period)	Priority and exploratory (sample size permitting) By number and type of asthma triggers	As described in Section 4.2.1.1	Adjusted rate ratios by Generalized Estimating Equation (GEE) and corresponding 95% CI for study vs. baseline period	4.2.1
Objective 2: To describe the time to first exacerbation after initiation of tezepelumab					
Secondary	Time to first asthma exacerbation	≥2 asthma exacerbations during the 12-month baseline period	As described in Section 4.2.1.1	Time to event Kaplan-Meier estimates	4.2.3
Objective 3: To describe asthma exacerbations resulting in hospitalization or ED/UC visits in the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period)					
Secondary	Rate of asthma exacerbations associated with hospitalizations over 52 weeks before (Baseline Period) and after initiation of tezepelumab	Priority and exploratory (sample size permitting)	As described in Section 4.2.1.1	Adjusted rate ratios by Generalized Estimating Equation (GEE) and corresponding 95% CI for Study vs. Baseline Period	4.2.3
Secondary	Rate of asthma exacerbations associated with ED/UC over 52 weeks before (Baseline Period)	Priority and exploratory (sample size permitting)	As described in Section 4.2.1.1	Adjusted rate ratios by Generalized Estimating Equation (GEE) and corresponding 95% CI for Study vs. Baseline Period	4.2.3

Statistical category	Endpoint	Subgroups to analyze	Intercurrent event strategy	Population level summary (analysis)	Details in section
	and after initiation of tezepelumab				
Secondary	Rate of asthma exacerbations associated with hospitalizations or ED/UC over 52 weeks before (Baseline Period) and after initiation of tezepelumab	Priority and exploratory (sample size permitting)	As described in Section 4.2.1.1	Adjusted rate ratios by Generalized Estimating Equation (GEE) and corresponding 95% CI for Study vs. Baseline Period	4.2.3
Objective 4: To describe lung function (pre-BD FEV1) at baseline and months 6 and 12 after initiation of tezepelumab					
Secondary	pre-BD FEV1	Baseline pre-BD FEV1 (% predicted) ≤ 80%; Phase 1 subgroups; Phase 2 subgroups; Baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 1 subgroups; Baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 2 subgroups; Baseline number of asthma trigger: ≥ 4; Baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Baseline number of asthma trigger: ≥ 4	As described in Section 4.2.1.1	Absolute values, and change from baseline by time point Descriptive statistics	4.2.4
Secondary	Change from baseline in pre-BD FEV1	Same as above	As described in Section 4.2.1.1	Adjusted change from baseline model for repeated measures	4.2.4

Statistical category	Endpoint	Subgroups to analyze	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary	Proportion of pre-BD FEV1 responders (defined as participants who achieve either at least a ≥5% or a 100 mL improvement from baseline)	Same as above	Not applicable	Total numbers and percentages	4.2.5
Objective 5: To describe asthma Control Questionnaire (ACQ-6), Asthma Impairment and Risk Questionnaire (AIRQ), and St. George's Respiratory Questionnaire (SGRQ) scores at baseline and months 6 and 12 after initiation of tezepelumab					
Secondary	ACQ-6, AIRQ and SGRQ (total and component) scores	ACQ-6: baseline ACQ-6 ≥ 1.5; Phase 1 subgroups; Phase 2 subgroups; ACQ-6 ≥ 1.5 among Phase 1 groups; ACQ-6 ≥ 1.5 among Phase 2 subgroups; Baseline ACQ-6 ≥ 1.5 and Visit 15 ACQ-6 ≥ 1.5; Baseline ACQ-6 ≥ 1.5 and Visit 15 ACQ-6 < 1.5; Baseline ACQ-6 ≥ 1.5 and Visit 8 ACQ-6 <1.5 and Visit 1.5 ACQ-6 < 1.5; Baseline number of asthma trigger: ≥ 4 AIRQ: baseline AIRQ ≥ 2; Phase 1 subgroups; Phase 2 subgroups;	As described in Section 4.2.1.1	Absolute values and change from baseline by time point	4.2.6

Statistical category	Endpoint	Subgroups to analyze	Intercurrent event strategy	Population level summary (analysis)	Details in section
		Baseline AIRQ ≥ 2 among Phase 1 subgroups; Baseline AIRQ ≥ 2 among Phase 2 subgroups; Baseline number of asthma trigger: ≥ 4 SGRQ: Phase 1 subgroups; Phase 2 subgroups; Baseline number of asthma trigger: ≥ 4			
Secondary	Change from baseline in ACQ-6, AIRQ and SGRQ (total and component) scores	Same as above	As described in Section 4.2.1.1	Adjusted change from baseline model for repeated measures	4.2.6
Secondary	Proportion of ACQ-6 responders (defined as participants who achieve ≥1 MCID)	Baseline ACQ-6 ≥ 1.5; Phase 1 subgroups; Phase 2 subgroups; ACQ-6 ≥ 1.5 among Phase 1 groups; ACQ-6 ≥ 1.5 among Phase 2 subgroups; Baseline ACQ-6 ≥ 1.5 and Visit 15 ACQ-6 ≥ 1.5; Baseline ACQ-6 ≥ 1.5 and Visit 15 ACQ-6 < 1.5; Baseline ACQ-6 ≥ 1.5 and Visit 8	Not applicable	Total numbers and percentages	4.2.7

Statistical category	Endpoint	Subgroups to analyze	Intercurrent event strategy	Population level summary (analysis)	Details in section
		ACQ-6 <1.5 and Visit 15 ACQ-6 < 1.5; Baseline number of asthma trigger: ≥ 4			
Secondary	Proportion by asthma control status (defined by ACQ-6)	Baseline ACQ-6 ≥ 1.5; Phase 1 subgroups; Phase 2 subgroups	Not applicable	Total number and percentages	4.2.7
Secondary	Proportion of AIRQ responders (defined as participants who achieve ≥1 MCID)	Baseline AIRQ ≥ 2; Phase 1 subgroups; Phase 2 subgroups; Baseline AIRQ ≥ 2 among Phase 1 subgroups; Baseline AIRQ ≥ 2 among Phase 2 subgroups; Baseline number of asthma trigger: ≥ 4	Not applicable	Total numbers and percentages	4.2.7
Secondary	Proportion by asthma control status (defined by AIRQ)	Baseline AIRQ ≥ 2; Phase 1 subgroups; Phase 2 subgroups	Not applicable	Total number and percentages	4.2.7
Secondary	Proportion of SGRQ total score responders (defined as participants who achieve ≥1 MCID)	Phase 1 subgroups; Phase 2 subgroups; Baseline number of asthma trigger: ≥ 4	Not applicable	Total numbers and percentages	4.2.7
Objective 6: To describe systemic corticosteroid (SCS) use in the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period)					
Secondary	Proportion of participants who require any SCS use	Phase 1 subgroups; Phase 2 subgroups	As described in section 4.2.8.2	Total numbers and percentages	4.2.8

Statistical category	Endpoint	Subgroups to analyze	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary	Cumulative annualized SCS dose	Phase 1 subgroups; Phase 2 subgroups	As described in section 4.2.8.2	Descriptive statistics Absolute values, percent change in % and change from baseline period by time point (study period) Adjusted change from baseline model for repeated measures Categorised percent reduction from the baseline period to the study period in cumulative OCS	4.2.8
Secondary	Proportion of participants who require longer-term (>30 consecutive days) SCS use	Phase 1 subgroups; Phase 2 subgroups	As described in section 4.2.8.2	Total numbers and percentages	4.2.8
Objective 7: To describe asthma-related healthcare resource utilization (HRU) in the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period)					
Secondary	Number and type of asthma-related HRU	Priority and exploratory (if sample size permitting) By number and type of asthma triggers	Not applicable	Total numbers and percentages	4.2.9
Secondary	Duration of asthma-related hospitalization	Priority and exploratory (if sample size permitting) By number and type of asthma triggers	Not applicable	Descriptive statistics	4.2.9

Statistical category	Endpoint	Subgroups to analyze	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 8: To describe adherence/persistence, duration of therapy, discontinuation, and reasons for discontinuation after initiation of tezepelumab					
Exploratory	Duration of tezepelumab treatment	Phase 1 subgroups; Phase 2 subgroups	Not applicable	Descriptive statistics	4.6.1
Exploratory	Frequency of discontinuation/interruption of tezepelumab treatment	Phase 1 subgroups; Phase 2 subgroups	Not applicable	Descriptive statistics	4.6.1
Exploratory	Time to discontinuation of tezepelumab treatment and reasons	Phase 1 subgroups; Phase 2 subgroups	Not applicable	Descriptive statistics	4.6.1
Exploratory	Number of administered tezepelumab injections	Phase 1 subgroups; Phase 2 subgroups	Not applicable	Descriptive statistics	4.6.1
Exploratory	Number of switches to other biologic for asthma treatments and biologics for asthma class	Phase 1 subgroups; Phase 2 subgroups	Not applicable	Descriptive statistics	4.6.1
Objective 9: To describe lung function (post-BD FEV1) at months 6 and 12 after initiation of tezepelumab					
Exploratory	post-BD FEV_1 value	Baseline pre-BD FEV1 (% predicted) ≤ 80%; Phase 1 subgroups; Phase 2 subgroups; Baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 1 subgroups; Baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 2 subgroups; Baseline number of asthma trigger: ≥ 4; Baseline Pre-BD	As described in Section 4.2.1.1	Absolute values and change from baseline by time point descriptive statistics	4.2.10

Statistical category	Endpoint	Subgroups to analyze	Intercurrent event strategy	Population level summary (analysis)	Details in section
		FEV1 (% Predicted) ≤ 80% among Baseline number of asthma trigger: ≥ 4			
Exploratory	FEV_1 reversibility	Same as above	As described in Section 4.2.1.1	Absolute values by time point descriptive statistics	4.2.11
Objective 10: To describe Treatment Satisfaction Questionnaire for Medication (TSQM-9) and physician clinical global impression of change (CGI-C) in months 6 and 12 after initiation of tezepelumab					
Exploratory	TSQM-9 score and CGI-C score	Phase 1 subgroups; Phase 2 subgroups	Not applicable	Absolute values by time point Number and percentage of TSQM-9 items summarised by time point	4.2.12
Objective 11: To describe frequent productive cough (FPC) at 6 and 12 months after initiation of tezepelumab					
Exploratory	FPC composite score	Among participants with baseline FPC; Severe asthma without COPD and baseline FPC; Mild and Moderate COPD and baseline FPC.	Not applicable	Total numbers and percentages by time point	4.2.13
Objective 12: To describe participants' assessment of their COPD symptoms in participants with COPD at 6 and 12 months after initiation of tezepelumab					
Exploratory	Patient's Global Impression of Change (PGIC) score for COPD	Comorbid COPD (see subgroup 6); comorbid mild COPD; comorbid moderate COPD.	Not applicable	Absolute value of total score by time point descriptive statistics Number and percentages of each item of the total score and each by time point	4.2.14
Objective 13: To describe total nasal symptom score (TNSS) at baseline and months 6 and 12 after initiation of tezepelumab					

Statistical category	Endpoint	Subgroups to analyze	Intercurrent event strategy	Population level summary (analysis)	Details in section
Exploratory	TNSS score	Among participants with baseline symptoms; Ongoing allergic rhinitis and baseline symptoms; CRS (wNP or sNP) and baseline symptoms; CRSwNP and baseline symptoms; CRSsNP and baseline symptoms	Not applicable	Absolute values and change from baseline by time point	4.2.15
Objective 14: To describe Sino-nasal Outcome Test (SNOT-22) at baseline and months 6 and 12 after initiation of tezepelumab					
Exploratory	SNOT-22 total score	CRS (CRSwNP and CRSsNP); CRSwNP (see subgroup 8); CRSsNP (see subgroup 25); CRSwNP with prior surgical history; CRSwNP without prior surgical history.	Not applicable	Absolute values and change from baseline by time point	4.2.16
Exploratory	Change from baseline in SNOT-22 score	Same as above	Not applicable	Adjusted change from baseline model for repeated measures	4.2.16
Exploratory	Proportion of SNOT-22 responders (defined as participants who achieve ≥1 MCID)	Same as above	Not applicable	Total numbers and percentages	4.2.17
Objective 15: To describe participant-reported causes of asthma symptoms or asthma attacks as reported within an asthma trigger survey at baseline and month 12, and asthma exacerbations and asthma-related HRU (sample permitting) during the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period) as a function of participant-reported trigger categories/number of reported triggers					

Statistical category	Endpoint	Subgroups to analyze	Intercurrent event strategy	Population level summary (analysis)	Details in section
Exploratory	Number and proportion of participants with reported trigger/number of triggers	Phase 1 subgroups; Phase 2 subgroups.	Not applicable	Total numbers and percentages	4.2.18
Exploratory	Change from baseline for reported triggers/number of triggers	Phase 1 subgroups; Phase 2 subgroups.	Not applicable	Descriptive statistics	4.2.18
Objective 16: To describe tezepelumab-treated participants meeting the study-specific definition of clinical remission					
Exploratory	Number and proportion of participants who achieve asthma clinical remission	Phase 1 subgroup; Phase 2 subgroup	Not applicable	Total numbers and percentages by time point	4.2.19
Objective 17: Qualitative interview data to explore participant experiences after initiation of tezepelumab across the sub-groups of selected participants					
Exploratory	Testimonials of treatment response	N/A	N/A	N/A	4.2.20

4.2.1 Primary Endpoint: Annualized Asthma Exacerbation Rate

4.2.1.1 Definition

Population: Adults and adolescents with asthma requiring medium-to high-dose inhaled corticosteroids (ICS), requiring additional controller(s), and those with at least 2 asthma exacerbations in the prior year who received at least one dose of tezepelumab

Endpoint: Asthma exacerbations in the 12-month periods before and after initiation of tezepelumab

Intercurrent events (ICE):

- Treatment discontinuation: All available data will be included for participants in the FAS.
- Initiation of other non-biologic medication for asthma: All available data will be included for participants in the FAS.
- Initiation of other biologics for asthma: All data after the start of another biologic for asthma will be deleted from the analyses.

Population-level summary: Annualized asthma exacerbation rate ratio and corresponding 95% CI for Study vs. Baseline Period

Study and Baseline Period are defined in Section 3.3.1.1. No formal hypothesis will be tested.

4.2.1.2 Derivations

The start and end date of the asthma exacerbation is collected in the EXACA eCRF. The asthma exacerbation duration is derived as

Exacerbation end date – Exacerbation start date + 1.

The AAER (in years) over the periods of interest (i.e. Baseline and Study periods) is calculated as the total number of asthma exacerbations over the 52-week Baseline Period or 52-week Study Period divided by the total time at risk calculated for the Baseline and Study periods, respectively. Derivation of time at risk over the Baseline or Study periods is detailed in two steps.

Step 1: Derivation of time at risk including time of asthma exacerbation

Table 4 Time at risk derivation over the 52-week study period

	If participant attends Visit 15 (Week 52)	If Visit 15 (Week 52) is not available for a participant
Time at risk over study period (52 weeks after initiation of tezepelumab)	[earliest (date of Visit 15[a], date of last exacerbation assessment status from EXACD eCRF, date of another biologic for asthma initiation) – Study Index date + 1]	[{earliest (Study Index date + 365 days + 5 days, date of last exacerbation assessment status from the EXACD eCRF, date of another biologic for asthma initiation) – Study Index date} + 1]

[a]The date of Visit 15 is used irrespective of how late this may have occurred in relation to the protocol schedule.

Time at risk for the 52-week Baseline Period is derived as

(Study Index date) – (date 52 weeks before Study Index date) +1.

Step 2: Derivation of time at risk excluding the time during an asthma exacerbation

The time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation cannot occur, is subtracted from the time at risk derivation over the Baseline and Study Periods defined in **Step 1** above.

Two or more exacerbations with the same start date and end date are counted as one exacerbation for the purposes of calculating the number and duration of exacerbations for a participant. In the case that one or more exacerbations are recorded as starting or ending during another exacerbation, these is 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 or urgent care visits requiring use of systemic corticosteroids (mg), or inpatient hospitalisation due to asthma occurring during an exacerbation is not regarded as a new exacerbation. To be counted as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled. If the end date of the first exacerbation or a temporary increase in a stable OCS background dose date, date of ED or urgent care visit, or date of hospital discharge and the start date of the second exacerbation are less than 7 days apart, then these is counted as one exacerbation.

It should be noted that the date of last assessment of exacerbation status from the eCRF might be later than the last available visit during the planned treatment period, in the case that the participant remained in the study with incomplete follow-up options after early discontinuation of the study intervention.

The exacerbations that occur after a participant has discontinued study intervention but before the end of the time at risk is still accounted when deriving the total number of exacerbations. Likewise, the time at risk reflects the time at risk regardless of whether the participant is still taking the study intervention or not.

Any exacerbation that starts within the time at risk but ends after this time point is included in analyses, with the end date adjusted to be no later than the time at risk. Any exacerbation that starts after the time at risk is not included in analyses.

Step 3: Derivation of overall time at risk

*Overall time at risk = time at risk **Step 2** / 365.25*

4.2.1.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.1.4 Primary Analysis of Primary Endpoint

The annualized asthma exacerbation rate as described in Section 4.2.1.2 will be calculated for the Baseline Period and the Study Period. Additionally, descriptive summaries will include the number and percentage of participants with asthma exacerbations, the total count of asthma exacerbations and the cumulative asthma exacerbation days before and after initiation of tezepelumab.

AAER in the Study Period will be compared to that seen in Baseline Period using a generalized estimating equations (GEE) model for repeated measures, using a log link function.

The response variable in the model will be the number of exacerbations in each period following negative binomial distribution. The covariates are period (Baseline Period, Study Period) and age (continuous). The logarithm of the time at risk is used as an offset variable. The unstructured covariance matrix is used. If the model will not converge, the compound symmetry matrix will be used. Before concluding non-convergence with any of the previous covariance structures, an attempt will be made to resolve convergence problems by using different starting values for the intercept.

In this model, inference will be based on generalized estimating equations (GEE). Participants will be included in the model using the REPEATED statement (not the RANDOM statement).

The annualized asthma exacerbation rate ratio for Study vs. Baseline Period will be obtained from the model by

Rate ratio = $\exp(\beta_{period})$.

As Baseline Period is set as the reference category, a rate ratio<1 indicates that the incidence rate of the Study Period is exp(β) times smaller than the incidence rate of the Baseline Period (or that in the Study Period it was shown [1-exp(β)]x100% reduction in AAER as compared to the Baseline Period). Summary results will include crude and

adjusted annualized asthma exacerbation rates for the Baseline and Study Period, the rate ratios and their corresponding 95% CIs and p-value.

Asthma exacerbations with start and end dates and the duration will be listed in a per-participant listing.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

In case there will be an extensive number of participants with 0 asthma exacerbation in the Study Period, an extension of the Poisson model with zero-inflation will be taken in account for a sensitivity analysis (Ridout et al 1998).

The Poisson model will include the same response variable and covariates as the GEE model described in Section 4.2.1.4.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

The number and percentage of participants with at least one exacerbation as well as with specific number of exacerbations (0, 1, 2, etc.) is presented. The total number of exacerbations, both overall and per participant, along with the cumulative exacerbation days per participant will be presented.

Exacerbation days is calculated as follows:

Exacerbation days = end date of exacerbation – start date of exacerbation +1

Cumulative exacerbation days is defined as the summation of exacerbation days and is calculated for the Baseline and Study Periods separately.

The number and percentage of participants with at least a 50% and a 100% reduction in asthma exacerbations at the end of week 52 following tezepelumab initiation will be summarized descriptively, respectively.

Absolute reduction in total number of asthma exacerbations per participant is calculated as follows:

Absolute reduction = (Count of asthma exacerbations during Study Period) – (Count of asthma exacerbations during Baseline Period)

Percentage reduction in number of asthma exacerbations per participant is calculated as follows:

Percentage reduction = [(Count of asthma exacerbations during Study Period) – (Count of asthma exacerbations during Baseline Period)] / (Count of asthma exacerbations during Baseline Period) x 100%

Asthma exacerbation reduction proportion

The number and percentage of participants who will reach at least a 50% or a 100% reduction in total number of asthma exacerbations during Study Period, respectively, and who completed the Study Period will be summarised descriptively. A participant will be considered to have completed the Study Period, if the Study Period is greater than 357 days (Day 364 minus 7, to account for visit windowing) and if the participant did not initiate treatment with other biologic for asthma.

4.2.1.7 Subgroup Analyses

The statistical analysis for the primary endpoint is presented by priority and by exploratory subgroups (permissible sample size is at least 10 participants per subgroup). The subgroups are defined in Section 3.3.1.4. The primary analysis model will be run separately for each defined subgroup and will include the same covariates as described in Section 4.2.1.4 (model will not include subgroup interaction terms).

The AAER over the Baseline and Study Periods is summarised descriptively by type of asthma triggers and number of asthma triggers. The number and percentage of participants with at least one exacerbation as well as with specific number of exacerbations (0, 1, 2, etc.) is similarly presented by type and number of asthma triggers. Furthermore, the cumulative number of asthma exacerbation days over the Baseline and Study Periods is summarised descriptively by type of asthma triggers and number of asthma triggers.

4.2.2 Secondary Endpoint: Time To First Asthma Exacerbation

4.2.2.1 Definition

The time to the first asthma exacerbation over the study period is presented.

4.2.2.2 Derivations

For participants who experienced an asthma exacerbation in the Study Period, time to first asthma exacerbation is calculated as follows:

Time to 1st exacerbation (days) = (Date of 1st asthma exacerbation in Study Period) – (index date) +1.

For participants who will not experience an asthma exacerbation in the Study Period or prior to initiation of another biologic for asthma, the time to first asthma exacerbation will be censored at the date of the earliest (date of initiation of another biologic for asthma, latest (last exacerbation assessment status from the EXACD eCRF, date of death)).

4.2.2.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.2.4 Primary Analysis of Secondary Endpoint

The time to first asthma exacerbation is calculated using Kaplan-Meier estimates. A Kaplan-Meier plot is presented as well as summary tables.

In addition, a figure will be produced to summarise the cumulative number of asthma exacerbations over the Study Period.

4.2.2.5 Supplementary Analyses of the Secondary Endpoint

No supplemental analysis will be performed.

4.2.2.6 Subgroup Analyses

Analysis will also be done for the subgroup: ≥2 asthma exacerbations during the 12-month baseline period.

4.2.3 Secondary Endpoint: Rate Of Asthma Exacerbations Resulting In Any Hospitalization, ED/Urgent Care Visit

4.2.3.1 Definition

Three rates of asthma exacerbations are assessed:

(i) Annualized rate of asthma exacerbations resulting in hospitalization only over the Baseline and Study Periods,

(ii) Annualized rate of asthma exacerbations resulting in ED/UC visits only over the Baseline and Study Periods,

(iii) Annualized rate of asthma exacerbations resulting in hospitalization or ED/UC visits over the Baseline and Study Periods.

Exacerbations resulting in hospitalization, ED/UC visits are a subset of all asthma exacerbations.

4.2.3.2 Derivations

All three endpoints are similarly derived to AAER including all asthma exacerbations as described in Section 4.2.1.2 but based on selected asthma exacerbations, i.e., resulting in hospitalization or ED/UC visit, resulting in hospitalization only, or resulting in ED/UC only.

4.2.3.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.3.4 Primary Analysis of Secondary Endpoint

The annualized asthma exacerbations rate for asthma exacerbations resulting in any hospitalization or ED/UC visit will be analysed in combination and separately (see Section 4.2.3.2) in the same way as described in Section 4.2.1.4.

4.2.3.5 Supplementary Analyses of the Secondary Endpoint

The number and percentage of participants with at least one exacerbation associated with hospitalizations or ED/UC visits over the Baseline and Study Periods as well as with specific number of exacerbations (0, 1, 2, etc.) is presented. The number of exacerbations associated with hospitalization or ED/UC visits per participant as well as cumulative exacerbation days and cumulative exacerbation days per participant is presented. The same approach for calculating exacerbation days and cumulative exacerbation days as described in Section 4.2.1.6 is applied for exacerbations associated with hospitalization or ED/UC visits.

4.2.3.6 Subgroup Analyses

Analyses will be presented for the priority and exploratory subgroups (permissible sample size is at least 10 participants per subgroup).

4.2.4 Secondary Endpoint: Change From Baseline in Pre-BD FEV_1 At 6 and 12 Months After Initiation of Tezepelumab

4.2.4.1 Definition

The change from baseline in pre-BD FEV1 is calculated at 6- and 12-months post initiation with tezepelumab.

4.2.4.2 Derivations

The absolute change from baseline in pre-BD FEV1 at a post-baseline visit is calculated as described in Section 3.3.1.7. Baseline value is derived as presented in Section 3.3.1.2. Strategies of handling intercurrent events are presented in Section 4.2.

4.2.4.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.4.4 Primary Analysis of Secondary Endpoint

Absolute values of pre-BD FEV_1, the percent change in % and absolute change from baseline will be summarized continuously by visit.

In addition, the absolute change from baseline at each post-baseline visit will be analysed using a model for repeated measures. Baseline pre-BD FEV1 and age will be included as continuous covariates, and visit will be included as a categorical covariate. Repeated measurements will be accounted for by including participant ID in the model using the REPEATED statement (no random effects are assumed).

The variance-covariance matrix is assumed to be unstructured. If the model will not converge, the compound symmetry matrix will be used. Before concluding non-convergence with any of the previous covariance structures, an attempt will be made to resolve convergence problems by using different starting values for the intercept. The Kenward-Roger approximation to estimating the degrees of freedom is used for tests of fixed effects derived from the model.

Adjusted means for visit from the model for repeated measures will be tabulated.

4.2.4.5 Supplementary Analyses of the Secondary Endpoint

No additional analysis.

4.2.4.6 Subgroup Analyses

Subgroups used for analysis are baseline pre-BD FEV1 (% predicted) ≤ 80%, Phase 1 and Phase 2 subgroups, baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 1 subgroups, baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 2 subgroups, baseline number of asthma trigger: ≥ 4 and baseline Pre-BD FEV1 (% Predicted) ≤ 80% among baseline number of asthma trigger: ≥ 4.

4.2.5 Secondary Endpoint: Pre-BD FEV_1 Responders At 6 and 12 Months After Initiation Of Tezepelumab

4.2.5.1 Definition

The proportion of pre-BD FEV1 responders are summarised at time points corresponding to the Schedule of Assessments in the CSP.

4.2.5.2 Derivations

Pre-BD FEV_1 responder/non-responder definition

Responders are defined as having

(Absolute change from baseline in pre-BD FEV_1) ≥ 100 mL

OR

(Percent change from baseline in pre-BD FEV_1) ≥ 5%.

Percent and absolute change are defined in Section 3.3.1.7.

Non-responders are defined as participants who neither have an absolute change from baseline in pre-BD FEV1 ≥100mL NOR percent change from baseline in pre-BD FEV1 ≥ 5%.

4.2.5.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.5.4 Primary Analysis of Secondary Endpoint

The number and proportion of pre-BD FEV1 responders, non-responders, and missing data are summarised over time.

4.2.5.5 Supplementary Analyses of the Secondary Endpoint

No additional analysis.

4.2.5.6 Subgroup Analyses

Subgroups used for analysis are baseline pre-BD FEV1 (% predicted) ≤ 80%, Phase 1 and Phase 2 subgroups, baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 1 subgroups, baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 2 subgroups, and baseline number of asthma trigger: ≥ 4 and baseline Pre-BD FEV1 (% Predicted) ≤ 80% among baseline number of asthma trigger: ≥ 4.

4.2.6 Secondary Endpoint: Change From Baseline In Asthma Questionnaires As 6 And 12 Months After Initiation Of Tezepelumab

4.2.6.1 Definition

The asthma questionnaires (ACQ-6, AIRQ, SGRQ) will be completed at time points as indicated in the Schedule of Assessments in the CSP.

ACQ-6

The ACQ-6 questionnaire includes 6 questions assessing the following concepts:

1. Awakening at night by symptoms
2. Limitations of normal daily activities
3. Waking in the morning with symptoms
4. Dyspnoea
5. Wheeze
6. Daily rescue medication

The questions are measured on a 7-point scale, are weighted equally, and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses.

Individual changes from baseline of ≥ 0.5 are considered to be clinically meaningful (minimum clinically important difference [MCID]). ACQ-6 responders in this study will be defined as participants who achieve ≥ 1 MCID.

AIRQ

The AIRQ has 10 questions that ask about respiratory symptoms, activity limitation, sleep, rescue medication use, social activities, exercise, difficulty controlling asthma, and exacerbations. All items have a yes/no response option and the tool is scored by counting the total number of 'yes' responses. This score is used to assess level of asthma control where: 0-1 is well controlled, 2-4 is not well controlled, and 5-10 is very poorly controlled. Thus, a higher score indicates worse control status (Murphy et al 2020).

The AIRQ items have 2 different recall periods: The first seven impairment items are evaluated over the past 2 weeks and the last three risk items over the past 3 months.

Individual changes from baseline of ≥ 2 are considered to be clinically meaningful (MCID). AIRQ responders in this study will be defined as participants who achieve ≥ 1 MCID.

SGRQ

The SGRQ is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into 2 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 3 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 domain scores range from 0 to 100, with higher scores indicative of greater impairment. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009).

Individual changes from baseline of ≥ 4 are considered to be clinically meaningful (MCID). SGRQ (total and component score) responders in this study will be defined as participants who achieve ≥ 1 MCID.

Absolute change from baseline to Visit 8 and to Visit 15 will be calculated for ACQ-6 score, AIRQ score, and SGRQ total and component scores as described in section 3.3.1.7.

4.2.6.2 Derivations

The absolute change from baseline in scores (ACQ-6, AIRQ, and SGRQ) at a post-baseline visit are calculated as described in Section 3.3.1.7. Baseline value is derived as presented in Section 3.3.1.2. Strategies of handling intercurrent events are presented in Section 4.2.

4.2.6.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.6.4 Primary Analysis of Secondary Endpoint

Absolute values of all scores (ACQ-6, AIRQ and SGRQ) and the absolute change from baseline will be summarized continuously by visit. Absolute changes from baseline for each score will be analysed using a model for repeated measures with the covariates including baseline score value, visit and age. All further steps described in Section 4.2.4.4 will be followed afterwards.

4.2.6.5 Supplementary Analyses of the Secondary Endpoint

Not applicable.

4.2.6.6 Subgroup Analyses

The following subgroup analyses will be performed:

- ACQ-6: Baseline ACQ-6 ≥ 1.5; Phase 1 and Phase 2 subgroups; ACQ-6 ≥ 1.5 among Phase 1 subgroups; ACQ-6 ≥ 1.5 among Phase 2 subgroups; Baseline ACQ-6 ≥ 1.5 and Visit 15 ACQ-6 ≥ 1.5; Baseline ACQ-6 ≥ 1.5 and Visit 15 ACQ-6 < 1.5; Baseline ACQ-6 ≥ 1.5 and Visit 8 ACQ-6 <1.5 and Visit 15 ACQ-6 < 1.5; Baseline number of asthma trigger: ≥ 4.

- AIRQ: Baseline AIRQ ≥ 2; Phase 1 and Phase 2 subgroups; Baseline AIRQ ≥ 2 among Phase 1 subgroups; Baseline AIRQ ≥ 2 among Phase 2 subgroups; Baseline number of asthma trigger: ≥ 4.

- SGRQ: Phase 1 and Phase 2 subgroups; Baseline number of asthma trigger: ≥ 4.

4.2.7 Secondary Endpoint: Asthma Questionnaire Responders At 6 And 12 Months After Initiation Of Tezepelumab

4.2.7.1 Definition

The asthma questionnaires (ACQ-6, AIRQ, SGRQ) will be completed at time points as indicated in the Schedule of Assessments in the CSP. For more information on ACQ-6, AIRQ, and SGRQ see Section 4.2.6.

4.2.7.2 Derivations

ACQ-6

Mean scores of ≤0.75 indicate well-controlled asthma, scores between 0.75 and ≤ 1.5 indicate partly controlled asthma, and scores >1.5 indicate not well controlled asthma. Individual changes of ≥0.5 are considered to be clinically meaningful (MCID).

- ACQ-6 responder definition: Absolute change from baseline in ACQ-6 ≤-0.5.
- ACQ-6 non-responder definition: Absolute change from baseline in ACQ-6>-0.5.

- ACQ-6 control definition: ACQ-6 < 1.5 at visit of interest.
- ACQ-6 uncontrolled definition: ACQ-6 ≥ 1.5 at visit of interest.

- Asthma control status at the visit of interest
  - Well-controlled asthma (ACQ-6 ≤ 0.75),
  - Partially controlled asthma (0.75<ACQ-6<1.5),
  - Poorly controlled asthma (ACQ-6 ≥ 1.5).

AIRQ

- AIRQ responder definition: Absolute change from baseline in AIRQ ≤-2.
- AIRQ non-responder definition: Absolute change from baseline in AIRQ>-2.

- Asthma control status at visit of interest:
  - Well-controlled (AIRQ = 0-1),
  - Not well-controlled (AIRQ = 2-4),
  - Very poorly controlled (AIRQ = 5-10).

SGRQ (total and component scores)

- SGRQ responder definition: Absolute change from baseline in SGRQ ≤-4.
- SRGQ non-responder definition: Absolute change from baseline in SGRQ>-4.

4.2.7.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.7.4 Primary Analysis of Secondary Endpoint

The number and percentages of ACQ-6, AIRQ, and SGRQ responders, non-responders, as well as ACQ-6 control and uncontrolled and asthma control status by ACQ-6 and AIRQ score are summarised separately over time.

4.2.7.5 Supplementary Analyses of the Secondary Endpoint

No additional analyses.

4.2.7.6 Subgroup Analyses

The following subgroup analyses for the responders will be performed:

- ACQ-6: Baseline ACQ-6 ≥ 1.5; Phase 1 and Phase 2 subgroups; ACQ-6 ≥ 1.5 among Phase 1 groups; ACQ-6 ≥ 1.5 among Phase 2 subgroups; Baseline ACQ-6 ≥ 1.5 and Visit 15 ACQ-6 ≥ 1.5; Baseline ACQ-6 ≥ 1.5 and Visit 15 ACQ-6 < 1.5;

Baseline ACQ-6 ≥ 1.5 and Visit 8 ACQ-6 <1.5 and Visit 15 ACQ-6 < 1.5; Baseline number of asthma trigger: ≥ 4.

- AIRQ: Baseline AIRQ ≥ 2; Phase 1 and Phase 2 subgroups; Baseline AIRQ ≥ 2 among Phase 1 subgroups; Baseline AIRQ ≥ 2 among Phase 2 subgroups; Baseline number of asthma trigger: ≥ 4.

- SGRQ: Phase 1 and Phase 2 subgroups; Baseline number of asthma trigger: ≥ 4.

Furthermore, for ACQ-6, and AIRQ asthma control status the subgroup analyses will be Phase 1 and Phase 2 subgroups.

4.2.8 Secondary Endpoint: Systemic Corticosteroid Use For Asthma

4.2.8.1 Definition

Assessment of SCS use for asthma over the baseline and study periods will be collected at time points as indicated in the Schedule of Assessments in the CSP in the Systemic Corticosteroids (mg) eCRFs.

4.2.8.2 Derivations

SCS use includes information on

- any SCS at any timepoint during Baseline Period and Study Period,
- cumulative annualized SCS dose (in prednisone equivalent dose, see Appendix 7.2) for Baseline Period and Study Period,
- long-term SCS use (>30 consecutive days) during Baseline Period and Study Period.

Data collected after initiation of another biologic for treatment of asthma is set to missing.

The endpoint is calculated using SCS medications collected on the ECSYSCRT eCRF page except SCS with a therapy reason of ‘Non-asthma condition’ and ‘Other’. All SCS are converted to a prednisone equivalent dose as described in Appendix 7.2.

Length of each prescribed SCS treatment

SCS treatment end date – SCS treatment start date + 1.

If the SCS treatment end date is “ongoing”, the last available date of the participant will be used.

Cumulative SCS dose (including length of treatment)

Baseline period

*Cumulative SCS dose = sum of (daily SCS dose*length of each prescribed SCS dose) over the baseline period*

Study period

*Cumulative SCS dose = sum of (daily SCS dose*length of each prescribed SCS dose) over the study period or earlier if another biologic for asthma reason is initiated*

Cumulative annualized SCS dose for each participant is calculated as followed:

*Cumulative annualized SCS dose = [sum of (cumulative SCS dose)/length of the planned treatment period]*365.25.*

4.2.8.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.8.4 Primary Analysis of Secondary Endpoint

The number and percentage of participants who requires any SCS use and who requires longer-term SCS use for the Baseline Period and during the Study Period is summarized descriptively. The cumulative annualized SCS dose is summarised using descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for the Baseline Period and Study Period.

In addition, the absolute values, absolute and percent change from baseline in the cumulative SCS dose is summarised using descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for the Baseline Period and Study Period.

Absolute change from baseline in cumulative SCS dose will be analysed using a General Linear Model. Change from baseline in cumulative SCS dose (between Study Period and Baseline Period) will be set as the response variable. Cumulative SCS over Baseline Period will be used as a continuous covariate. The LS mean estimate and corresponding 95% CIs will be presented.

The percentage change from baseline in cumulative SCS will be categorised as follows: ≤0%, >0%, >0% to <25%, ≥25% to <50%, ≥50% to <75%, ≥75% to ≤100%. The number and percentage of participants within the categories will be presented as well as a two-sided 95% CI for proportions computed using exact Clopper-Pearson method.

4.2.8.5 Subgroup Analyses

Subgroups used for analysis are Phase 1 and Phase 2 subgroups and the baseline number of asthma triggers ≥4.

4.2.9 Secondary Endpoint: Asthma-related Healthcare Resource Utilization

4.2.9.1 Definition

Asthma-related HRU over the Baseline and Study Periods will be collected at time points as indicated in the Schedule of Assessments in the CSP in the Asthma-related HRU eCRF.

4.2.9.2 Derivations

Number and type of asthma-related HRU per participant (inpatient and outpatient) including:

- any HRU associated with asthma exacerbation,
- ER visit/urgent care visit or inpatient hospitalization,
- unscheduled HCP visit/telephone consultations,
- exacerbation-related SCS courses,
- exacerbation-related antibiotic courses.

Length of stay in hospital in days

(Discharge date – admission date +1),

The same applies for length of stay within a specific ward.

The annual rate of hospitalization is calculated as total number of days in hospitalization*365.25/Sum over all subjects (last follow-up date - Visit 2 date + 1).

Annual rate of resource utilisation = Number of HRU events*365.25 / Sum over all subjects (last follow-up date - Visit 2 date + 1).

4.2.9.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.9.4 Primary Analysis of Secondary Endpoint

Total numbers and percentages of participants with any asthma-related HRU and the specific type of asthma-related HRU will be summarized for the Baseline Period and for the Study Period. The total counts of any type of asthma-related HRU will be summarized for the Baseline Period and the Study Period. The number and percentage of participants who will have at least one HRU less during the Study Period compared to the Baseline Period

will be reported in addition. Length of stay in hospital and in any specific ward will be analysed with descriptive statistics for continuous data.

The health care resource utilization rates in the Study Period will be compared to that seen in Baseline Period using a generalized estimating equations (GEE) model for repeated measures, using a log link function. Two models will be estimated, where for the first model the response variable in the model will be the number of HRU events in each period, while for the second model the response variable in the model will be the number of hospitalisation days following negative binomial distribution. The covariate is period (Baseline Period, Study Period) and age (continuous). The logarithm of the follow- up time is used as an offset variable. The unstructured covariance matrix is used. If the model will not converge, the compound symmetry matrix will be used. Before concluding non-convergence with any of the previous covariance structures, an attempt will be made to resolve convergence problems by using different starting values for the intercept.

In this model, inference will be based on generalized estimating equations (GEE). Participants will be included in the model using the REPEATED statement (not the RANDOM statement).

The rate ratio for Study vs. Baseline Period will be obtained from the model by Rate ratio = $\exp(\beta_{period})$.

As Baseline Period is set as the reference category, a rate ratio<1 indicates that the incidence rate of the Study Period is exp(β) times smaller than the incidence rate of the Baseline Period (or that in the Study Period it was shown [1-exp(β)]x100% reduction in resource utilisation annual rate compared to the Baseline Period). Summary results will include crude and resource utilisation annual rate for the Baseline and Study Period, the rate ratios and their corresponding 95% CIs and p-value.

4.2.9.5 Subgroup Analyses

All statistical analyses for asthma-related HRU will be summarized by priority and exploratory subgroups (if sample size permitting). Additionally, all analyses for asthma-related HRU will be summarized by the type and number of asthma triggers.

4.2.10 Exploratory Endpoint: Change From Baseline In Post-BD FEV_1 At 6 And 12 Months After Initiation With Tezepelumab

4.2.10.1 Definition

The change from baseline in post-bronchodilator FEV_1 is calculated at time points as indicated in the Schedule of Assessments in the CSP.

4.2.10.2 Derivations

The absolute change from baseline in post-BD FEV_1 at a post-baseline visit is calculated as described in Section 3.3.1.7 on the FAS. Baseline value is derived as presented in Section 3.3.1.2. Strategies of handling intercurrent events are presented in Section 4.2

4.2.10.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.10.4 Primary Analysis of Post-BD FEV_1

Absolute values and change from baseline in post-BD FEV_1 will be summarized descriptively by time point.

4.2.10.5 Subgroup Analyses

Subgroups used for analysis are baseline pre-BD FEV1 (% predicted) ≤ 80%, Phase 1 and Phase 2 subgroups, baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 1 subgroups, baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 2 subgroups, baseline number of asthma trigger: ≥ 4 and baseline Pre-BD FEV1 (% Predicted) ≤ 80% among baseline number of asthma trigger: ≥ 4.

4.2.11 Exploratory Endpoint: Percent Reversibility At 6 And 12 Months After Initiation With Tezepelumab

4.2.11.1 Definition

Percentage reversibility is calculated at 6 and 12 months after initiation with tezepelumab.

4.2.11.2 Derivations

Percentage reversibility is defined as follows, for pre-BD and post-BD measurements taken on the same date:

% Reversibility = [(Post-BD FEV_1 – Pre-BD FEV_1)/Pre-BD FEV_1] x 100%

4.2.11.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.11.4 Primary analysis of Post-BD FEV_1 reversibility

Percent reversibility will be summarised descriptively by time point.

4.2.11.5 Subgroup Analyses

Subgroups used for analysis are baseline pre-BD FEV1 (% predicted) ≤ 80%, Phase 1 and Phase 2 subgroups, baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 1 subgroups, baseline Pre-BD FEV1 (% Predicted) ≤ 80% among Phase 2 subgroups, baseline number of asthma trigger: ≥ 4 and baseline Pre-BD FEV1 (% Predicted) ≤ 80% among baseline number of asthma trigger: ≥ 4.

4.2.12 Exploratory Endpoint: Treatment Satisfaction Questionnaire from Medication (TSQM-9) And Physician Clinical Global Impression of Change (CGI-C)

4.2.12.1 Definition

TSQM-9 and CGI-C will be collected at time points as indicated in the Schedule of Assessments in the CSP.

TSQM-9

The TSQM-9 is a questionnaire developed to provide a measure of treatment satisfaction with medication, providing scores on three domains: effectiveness, convenience and global satisfaction. The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain.

The TSQM-9 domain scores from baseline to 6 and 12 months after the initiation of tezepelumab are calculated.

CGI-C

The Clinical Global Impression of Change (CGI-C) will be used to evaluate the overall response to treatment. The Investigator (clinician) will be asked to rate the degree to which the overall asthma status may have changed when compared to baseline. The assessment uses a 7-point rating scale: 1 = Very Much Improved; 2 = Much Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; and 7 = Very Much Worse. The CGI-C will be completed at the site by the Investigator.

The CGI-C score at 6 and 12 months after the initiation of tezepelumab is calculated.

4.2.12.2 Derivations

TSQM-9

The 3 individual domain scores (effectiveness, convenience and global satisfaction) are calculated as the means of responses to the questions in each of the domains. Higher scores indicate better outcomes.

CGI-C

No score derivation is necessary as the score will be equal to the Investigator (clinician) evaluation on the 7-point scale. Higher score indicates worse outcomes.

4.2.12.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.12.4 Primary Analysis of TSQM-9 and CGI-C

The domain scores of TSQM-9 and total score of CGI-C will be analysed descriptively by time point. Additionally, number and percentages of the items of TSQM-9 will be summarized by time point.

4.2.12.5 Subgroup Analyses

Subgroups used for analysis are Phase 1 and Phase 2 subgroups.

4.2.13 Exploratory Endpoint: Change From Baseline in Frequent Productive Cough (FPC) At 6 And 12 Months After Initiation Of Tezepelumab

4.2.13.1 Definition

FPC is a binary composite endpoint based on SGRQ and consists of the categories “having FPC” or “not having FPC”.

FPC will be calculated using two St. George’s Respiratory Questionnaire (SGRQ) items: “Over the past 3 months, I have coughed…” and “Over the past 3 months, I have brought up phlegm (sputum)…”. Responses to these items range from 0 to 4 (“Not at all” – 0, “Only with respiratory infections” – 1, “A few days a month” – 2, “Several days a week” – 3, and “Almost every day” – 4).

4.2.13.2 Derivations

FPC score is defined as the unweighted sum of the responses to the two SGRQ items identified in Section 4.2.6.

- Having FPC definition: FPC composite score ≥ 3,
- Not having FPC definition: FPC composite score < 3.

4.2.13.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.13.4 Primary Analysis of FPC

The number and percentages of subjects having FPC, not having FPC, and missing data are summarised descriptively at baseline, Visit 8, and Visit 15.

4.2.13.5 Subgroup Analyses

The following subgroup analyses will be performed: participants with baseline FPC; Severe asthma without COPD and baseline FPC; Mild and Moderate COPD and baseline FPC.

4.2.14 Exploratory Endpoint: Patient's Global Impression of Change (PGI-C) Score for COPD

4.2.14.1 Definition

The PGI-C scale is used to measure change in clinical status. In this study only participants with COPD will be asked to complete this scale to determine if there has been an improvement or decline in their disease. The assessment uses a 7-point rating scale: 1 = Much better; 2 = Moderately better; 3 = A little better; 4 = About the same; 5 = A little worse; 6 = Moderately worse; and 7 = Much worse.

4.2.14.2 Derivations

The PGI-C score will be completed at time points as indicated in the Schedule of Assessments in the CSP and is equal to the outcome of the 7-point rating scale. Higher scores indicate worse outcomes.

4.2.14.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.14.4 Primary Analysis of PGI-C

The total score of PGI-C will be summarized with descriptive statistics by time point for participants with comorbid COPD. Additionally, the total number and percentage of each item will be summarized by time point.

4.2.14.5 Subgroup Analyses

Subgroups used for the PGI-C analysis are comorbid COPD; comorbid mild COPD; and comorbid moderate COPD.

4.2.15 Exploratory Endpoint: Total Nasal Symptom Score (TNSS)

4.2.15.1 Definition

The TNSS will be completed by all participants and is a brief questionnaire which evaluates the severity of main symptoms of allergic rhinitis. A total score is the sum of at least 3 of the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing. Each question can be answered using a 4-point scale from 0 (no symptoms) up to 3 (severe symptoms) (Downie et al., 2004).

4.2.15.2 Derivations

The absolute change from baseline in TNSS at a post-baseline visit is calculated as described in Section 3.3.1.7 for participants with baseline symptoms. Participants with baseline symptoms are defined as those with a baseline TNSS score greater than or equal to 1. Baseline value is derived as presented in Section 3.3.1.2.

4.2.15.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.15.4 Primary Analysis of TNSS

Absolute values and change from baseline by time point will be summarized descriptively.

4.2.15.5 Subgroup Analyses

The following subgroup analyses will be performed:

- Participants with baseline symptoms, Allergic rhinitis and baseline symptoms, CRS (wNP or sNP) and baseline symptoms, CRSwNP and baseline symptoms, and CRSsNP and baseline symptoms.

4.2.16 Exploratory Endpoint: Sino-Nasal Outcome Test (SNOT-22)

4.2.16.1 Definition

The SNOT-22 is a 22-item PRO for sinonasal conditions (Hopkins et al 2009) and will be completed by participants with comorbid CRSwNP and CRSsNP at baseline. The tool is a modification of the SNOT-20 (Piccirillo et al 2002) where items related to nasal blockage and loss of sense of tastes and smell have been added and the importance rating has been removed. The 22-item SNOT-22 is scored as 0 (no problem) to 5 (problem as bad as it can be) with a total range from 0 to 110 (higher scores indicate poorer outcomes) (Hopkins et al 2009). Individual changes from baseline of ≤ 8.9 are considered to be clinically meaningful (MCID). SNOT-22 responders in this study will be defined as participants who achieve ≥ 1 MCID.

4.2.16.2 Derivations

The absolute change from baseline in SNOT-22 at a post-baseline visit is calculated as described in Section 3.3.1.7. Baseline value is derived as presented in Section 3.3.1.2.

4.2.16.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.16.4 Primary Analysis of SNOT-22

Absolute values and change from baseline by time point will be summarized descriptively.

4.2.16.5 Subgroup Analyses

CRS (CRSwNP and CRSsNP); CRSwNP (see subgroup 8); CRSsNP (see subgroup 25); CRSwNP with prior surgical history; CRSwNP without prior surgical history.

4.2.17 Exploratory Endpoint: SNOT-22 Responders

4.2.17.1 Definition

The SNOT-22 will be completed at Visit 2 prior to tezepelumab initiation, at time points as indicated in the Schedule of Assessments in the CSP. For more information on SNOT-22, see Section 4.2.16.

4.2.17.2 Derivations

SNOT-22 responder

- SNOT-22 responder definition: Absolute change from baseline in SNOT-22≤-8.9.
- SNOT-22 non-responder definition: Absolute change from baseline in SNOT-22>-8.9.

4.2.17.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.17.4 Primary Analysis of SNOT-22 responders

The number and percentages of SNOT-22 responders, non-responders, and missing data are summarised descriptively over time. Absolute values and change from baseline to Visit 8 and Visit 15 by time point will be summarized descriptively. Absolute change from baseline for SNOT-22 score will be analysed using a model for repeated measures with the covariates including baseline score value, visit (Visit 8 and Visit 15) and age. Repeated measurements will be accounted for by including subject ID in the model using the REPEATED statement (no random effects are assumed). The least squares means, 95% CI, standard error and p-value will be reported.

4.2.17.5 Subgroup Analyses

CRS (CRSwNP and CRSsNP); CRSwNP (see subgroup 8); CRSsNP (see subgroup 25); CRSwNP with prior surgical history; CRSwNP without prior surgical history.

4.2.18 Exploratory Endpoint: Asthma Trigger Survey

4.2.18.1 Definition

The asthma trigger survey will be completed at time points as indicated in the Schedule of Assessments in the CSP.

The asthma trigger survey is a one question survey administered to collect data on the activities and/or other factors that trigger asthma symptoms and/or attacks. The information collected through the survey will provide participant-generated insights on what factors triggers symptoms or exacerbations.

4.2.18.2 Derivations

The total number of asthma triggers will be counted during the Baseline and Study Periods. The change in number of reported triggers is defined as:

Change in triggers = Number of reported triggers in study period – number of reported triggers in baseline period

4.2.18.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.18.4 Primary Analysis of Asthma Trigger Survey

Number and percentage of participants with any reported trigger and type of trigger will be summarized at the Baseline Period and during the Study Period. Additionally, the total count of asthma triggers per participant will be summarized for both periods. Change from baseline will be calculated for each type of reported trigger and for the total count of triggers.

All data collected in the asthma trigger survey will be listed.

4.2.18.5 Subgroup Analyses

Subgroups used for analysis are Phase 1 and Phase 2 subgroups.

4.2.19 Exploratory Endpoint: Asthma Clinical Remission

4.2.19.1 Definition

Asthma clinical remission on tezepelumab will be evaluated between Visit 2 and Visit 8 and between Visit 2 and Visit 15. The definition of clinical remission is based on ACQ-6, lung function, OCS status and exacerbation criteria defined in Table 4.

4.2.19.2 Derivations

Only those subjects who complete the visit and have available data for the time period of interest (Visit 15) will be included in the analysis. A participant will reach clinical remission if all four conditions are met. Participants who will not fulfil the criteria for clinical remission will be considered as not having reached clinical remission. Table 4 below shows two definitions for clinical remission, where the only difference is the condition of ACQ-6.

Table 4 Criteria for defining clinical remission

Condition 1: ACQ-6	Condition 2: Lung function	Condition 3: Daily OCS use for asthma	Condition 4: Exacerbations
ACQ-6 at post-baseline visit	**Lung function at post-baseline visit**	**Daily OCS use at post-baseline visit**	**Exacerbations after tezepelumab initiation**
< 1.5	$\frac{\text{pre-BD FEV1 (L)}}{\text{pre-BD FEV1 (L) at BL}} \geq 0.95$	No	No
≤ 0.75	$\frac{\text{pre-BD FEV1 (L)}}{\text{pre-BD FEV1 (L) at BL}} \geq 0.95$	No	No

BL = baseline, BD=bronchodilator

The number and percentage of participants obtaining asthma clinical remission at Visit 15 will be summarized for the criteria below, for participants in the FAS:

- Individual components of clinical remission:
  - No exacerbations
  - No daily OCS use
  - pre-BD FEV1 (L) at post-baseline /(pre-BD FEV1 (L) at baseline) ≥ 0.95
  - ACQ-6 score < 1.5
  - ACQ-6 score ≤ 0.75
- Combinations of individual components of clinical remission
  - No exacerbations and no daily OCS use
  - No exacerbations, no daily OCS use, and ACQ-6 score < 1.5
  - No exacerbations, no daily OCS use, and ACQ-6 score ≤ 0.75
- Clinical remission
  - No exacerbations, no daily OCS use, ACQ-6 score < 1.5, and pre-BD FEV1 (L)/(pre-BD FEV1 (L) at baseline) ≥ 0.95
  - No exacerbations, no daily OCS use, ACQ-6 score ≤ 0.75, and pre-BD FEV1 (L)/(pre-BD FEV1 (L) at baseline) ≥ 0.95
- No exacerbations, no daily OCS use, ACQ-6 score < 1.5, and predicted pre-BD FEV1 of ≥ 80%

- Participants who achieve clinical response with at least one of the following criteria at Visit 15 from the baseline period:
  - ≥50% reduction in asthma exacerbations,
  - ≥50% reduction in daily OCS use,
  - change from baseline in the ACQ-6 score ≥–0.5, OR
  - ≥100 mL change in pre-BD FEV1.

4.2.19.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.19.4 Primary Analysis of Asthma Clinical Remission

Clinical remission will be evaluated at Week 24 (Visit 8) and at Week 52 (Visit 15). The number and percentage of participants obtaining asthma clinical remission at Visit 8 or at Visit 15 will be summarized for all four criteria in Table 4 for participants in the FAS. A cross tabulation of clinical remission status at Visit 8 vs Visit 15 will also be presented. Clinical remission status will be listed including the criteria defining clinical remission.

4.2.19.5 Subgroup Analyses

Subgroups used for analysis are Phase 1 and Phase 2 subgroups.

4.2.20 Exploratory Endpoint: Qualitative Participants' Interview

Participant experience interviews will be conducted with up to 50 participants at the end of the Study Period (Visit 15), or at an Early Termination Visit for participants who may not participate in the study until follow-up. Interviews will be semi-structured and non-interventional.

No statistical analysis is planned for the qualitative participants' interview. Results will be summarized in a separate report.

4.3 Pharmacodynamic Endpoint

Not Applicable.

4.4 Pharmacokinetics

Not applicable.

4.5 Immunogenicity

Not applicable.

4.6 Safety Analyses

Safety and tolerability of tezepelumab is assessed from serious adverse events (SAEs), SAEs with outcome of death, adverse events leading to discontinuation of study

intervention (DAEs), adverse events of special interest (AESIs), and laboratory tests. All safety analyses, including per-participant listings, will be summarised using the FAS.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Extent of exposure

Exposure to study drug is expressed as the duration of study treatment in days. This is defined as the number of days between the date of first dose of study intervention and the date of last dose of study intervention for participants who completed the study. For participants who discontinue treatment prematurely or are withdrawn from study the date of Early Termination Visit will be used. For participants who die the date of death will be used:

Extent of exposure (days) = minimum (date of last dose of study intervention + 35 days, date of Early Termination Visit, date of Death) – (date of first dose of study intervention) + 1.

This calculation does not consider any intermediate missing administrations of study drug caused by the participant. Interruptions of study treatment will be identified in the eCRF if they occur and will be counted separately in the analysis.

Time to premature discontinuation of tezepelumab treatment

This will be only calculated for participants with an Early Termination Visit.

Time to study treatment discontinuation (days) = (Date of last dose of study intervention) – (Date of first dose of study intervention) +1.

4.6.1.2 Presentation

The duration of tezepelumab treatment per participant will be summarized descriptively for the FAS. In a further summary table, the following details on exposure will be shown:

- the number of administrations of study drug per participant,
- number of participants with interruptions of tezepelumab treatment,
- interruptions of tezepelumab treatment in categories (1,2,3,…),
- time to discontinuation of tezepelumab,
- number of switches to other biologic treatment of asthma and biologics class for asthma.

The date and time of study drug administrations and missed doses will be listed for the FAS.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

Only events that fall into the following categories will be collected in this study

- serious AEs (see CSP Appendix B2),
- AEs leading to discontinuation of tezepelumab (DAEs),
- AEs of special interest (AESI):
  - serious hypersensitivity reactions,
  - serious infections,
  - Helminth infections (serious or non-serious),
  - All malignancies (Note: all malignancies will be considered 'serious' and reported as SAEs accordingly),
  - Guillain Barre Syndrome (serious or non-serious),
  - serious cardiac events.

An AE of special interest (AESI) is an event of scientific and medical interest towards improving the understanding of tezepelumab. An AESI may be serious or non-serious. An AESI that meets one of the seriousness outcomes will be categorized as an SAE for the purposes of follow-up responsibility and safety reporting. More details on AESI can be found in the Appendix 7.1.

If an AE has a missing onset date completely, it is considered an on-treatment event unless the stop date of the AE indicates otherwise. Similarly, if an AE has a partial onset date, it is considered an on-treatment AE unless the partial onset date or the stop date indicates otherwise.

Events with missing relationship will be considered as 'related to study drug' for summary purposes but will be recorded as missing in the listings. In summaries of the maximum intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Participants who experience the same event multiple times, with differing severities, will be included in the most severe category.

Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings. Participants with multiple occurrences are counted once per system organ class and preferred term regardless of the number of occurrences.

Adjusted incidence rate

Exposure-adjusted incidence rate is defined as the total number of participants reporting adverse events experienced during the extent of exposure divided by total extent of exposure (irrespective of whether they have had the AE). The individual participant's

extent of exposure (days) is calculated as presented in Section 4.6.1.1. The total participant-years exposure is derived as the sum of the individual participant extent of exposure (days) divided by 365.25.

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

In the above summaries, the exposure-adjusted incidence rate (EAIR) will be calculated for each treatment as the number of participants in that treatment group reporting the AE divided by the total time at risk in that treatment group, where time at risk is the time to the first event for a participant who experienced the event during the analysis period and time during the study period for a participant who didn't experience the event. EAIR will be reported as events per 100 participant-years.

4.6.2.2 Presentation

Only AEs occurring on-treatment according to the definition in section 3.3.1.1 will be summarized. Adverse events occurring during the screening period or occurring post-treatment are listed but not summarized separately.

An overall summary table will be produced showing the number and percentage of participants with at least one AE in each of the following categories: SAEs, SAEs with an outcome of death, DAEs. The number of participants with AEs in the different AE categories will be presented for the FAS.

Also, all AEs categories will be summarised by system organ class (SOC) and preferred term (PT) assigned to the event using the MedDRA dictionary. For each PT, the number and percentage of participants reporting at least one occurrence of the event will be presented.

These summary tables will be presented by subgroups: adults and adolescents (in Section 3.3.1.4).

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

- SAEs,
- SAEs with an outcome of death,
- DAEs,
- each AESI category separately.

All AEs (by PT) will be summarised additionally by causality and maximum intensity.

An overview table showing the preferred terms mapped to each AESI will be presented. All AEs in the different categories will also be listed for FAS. Details on Helminth infections, infection diagnostic, infection risk factors and signs and symptoms of infection will be listed.

Key subject information of SAEs, DAEs, and AESIs for the on-treatment period is presented.

The number and percentage of participants reporting COVID-19 AEs (as defined on the COVID-19 MedDRA terms) is summarised by System Organ Class (SOC) and Preferred Term (PT) for the on-treatment period.

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

All summaries are presented on the FAS.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Most of the hematology and clinical chemistry assessments will be performed at Screening or before tezepelumab dosing at Visit 2 and sent to the local laboratories at the sites. Only absolute blood eosinophil count (1/uL), total Immunoglobulin E (IgE) (kU/L) and perennial allergen-specific IgEs (kU/L) will be collected prior to the first dose of study intervention (Visit 2) and additionally at the last study visit (Visit 15). A list of laboratory variables for this study can be found in the CSP section 8.5.3, Table 5.

4.6.3.2 Presentations

Blood eosinophil count (1/uL) and total and perennial allergen-specific IgE are summarized by descriptive statistics over both time points. Also, the change from baseline to last study visit will be calculated for these lab parameters.

For all available hematology and clinical chemistry parameters, the frequency of clinically noteworthy values (using normal reference ranges) occurring during the study are presented. No further summaries will be presented for the other hematology and clinical chemistry parameters.

All summary tables are presented for the FAS.

4.6.4 Clinical Laboratory, Urinalysis

Not applicable.

4.6.5 Other Laboratory Evaluations

Not applicable.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Weight and height will be measured at Visit 1 or Visit 2. Additionally, weight will only be measured at Visit 15. Body mass index will be calculated but not captured in the eCRF. Absolute change from baseline is calculated as described in Section 3.3.1.7.

4.6.6.2 Presentations

Observed values of weight, height, and BMI are summarised at each timepoint they are measured using descriptive statistics. Absolute change from baseline for weight and BMI are also presented over time.

4.6.7 Electrocardiogram

Not applicable.

4.6.8 Other Safety Assessments

X-rays and CT scans are not study procedures per protocol, but data on these examinations will be collected in the eCRF. X-rays and CT scans will be collected at Visit 1, Visit 8, Visit 15, and Early Termination Visit. This data will be included in listings with the date and time of assessment and a flag for abnormal and clinically significant findings for the FAS.

5 INTERIM ANALYSIS

One or more interim analyses may be conducted at any time at the discretion of the sponsor for the purpose of describing interim results and potentially supporting study publications. The results of the interim analysis will not be used to change any element of the study design, and the study will continue regardless of the results of interim analysis. The interim analysis is not powered and should not be the reason for any study design changes.

The interim analyses details are included in the d5180c00032-sap-passage-IA2.

Some of the critical analyses described in this SAP will be conducted for the interim analyses as far as possible. The analyses to be conducted will depend on the type of data displays needed for abstracts/poster presentations and the extent of the data that is available. Participants who have not completed the study in an interim analysis will go into the analysis as ongoing in study and be analysed to the extent possible.

There will be approximately 400 participants included in the study and most of the statistical analyses will be applied to data collected at Visit 8 and Visit 15.

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7 APPENDIX

7.1 Adverse events of special interest

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 are finalised by the study team prior to unblinding of the trial and provided together with the study datasets at the time of submission.

AESIs defined based on MedDRA term

The following MedDRA term selection criteria is currently being used for defining the AESI:

- Serious hypersensitivity reactions – MedDRA SMQ “Hypersensitivity” – narrow
- Serious infections (including opportunistic infections) – all terms in MedDRA System Organ Class “Infections and infestations”
- Malignancy – based on SMQ “Malignant or unspecified tumours”
- Guillain-Barre Syndrome – based on SMQ Guillain-Barre syndrome

Helminth infection

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

A participant is considered to have this AESI if the participant 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.

Serious cardiac events

Serious cardiac event is directly determined from what is entered on the eCRF.

7.2 OCS conversion factors for prednisone equivalents

Total daily OCS dose will be converted to a prednisone equivalent using the following table:

Table 5 Estimated OCS dose therapy equivalence dose

Oral Corticosteroid	Approximate equivalence dose
Prednisone	10 mg
Prednisolone	10 mg
Cortisone	50 mg
Hydrocortisone	40 mg
Methylprednisolone	8 mg
Triamcinolone	8 mg
Betamethasone	1.2 mg
Dexamethasone	1.5 mg
Deflazacort	12 mg

For example, to convert a cortisone total daily dose to a prednisone equivalent total daily dose, a multiplication factor of 0.2 = 10/50 should be used.

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Statistical Analysis Plan PASSAGE Edition 3

Approval Signatures

Document Name: Statistical Analysis Plan 27 Jun 2025 D5180C00032

Document Number: VV-TMF-9527287

Parexel Version Number:

System Version Number: 1 .0

Document Approvals	
Reason for signing: Approved	Name: PPD Role: PPD Date of signature: 27-Jun-2025 08:10:23 GMT+0000