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Study Title: A Multicentre, Single-arm, Phase 3b Efficacy and Safety Study of Tezepelumab 210 mg Administered Subcutaneously to Reduce Oral Corticosteroid Use in Adult Participants with Severe Asthma on High-dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Long-term Oral Corticosteroid Therapy (WAYFINDER)

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A Multicentre, Single-arm, Phase 3b Efficacy and Safety Study of Tezepelumab 210 mg Administered Subcutaneously to Reduce Oral Corticosteroid Use in Adult Participants with Severe Asthma on High-dose Inhaled Corticosteroid plus Long-acting β_2 Agonist and Long-term Oral Corticosteroid Therapy (WAYFINDER)

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LIST OF ABBREVIATIONS

List abbreviations and definitions of specialized or unusual terms, measurements, or units.

Abbreviation or Specialized Term	Definition
AAER	Annualised asthma exacerbation rate
ACQ-6	Asthma Control Questionnaire 6
AE	Adverse event
AESI	Adverse Event of Special Interest
AI	Adrenal Insufficiency
AIRQ	Asthma Impairment and Risk Questionnaire
ALT	Alanine aminotransferase
AQLQ(s)+12	Standardised Asthma Quality of Life Questionnaire for 12 years and older
AST	Aspartate aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
DCO	Data Cut Off
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAE	Discontinuation of investigational product due to adverse event
DBL	Database Lock
eCRF	Electronic Case Report Form
EOS	Eosinophil
EOT	End of Treatment
ePRO	Electronic participant-reported outcome device
ER	Emergency Room
FAS	Full Analysis Set
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced Expiratory Volume in 1 second
GAM	Generalized Additive Model
HCG	Human Chorionic Gonadotropin
HL	Hy's Law
IA	Interim Analysis
IgE	Immunoglobulin E
IMP	Investigational Medicinal Product

IP	Investigational Product
IPD	Investigational Product Discontinuation
LABA	Long-acting β_2 agonist
LOESS	Locally Estimated Scatterplot Smoothing
MedDRA	Medical Dictionary for Regulatory Activities
MICD	Minimal Clinically Important Difference
NA	Not Applicable
OCS	Oral Corticosteroids
PHL	Potential Hy's Law
PD	Protocol Deviation
PI	Principal Investigator
PK	Pharmacokinetics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of Activities
ULN	Upper Limit of Normal
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	10-Mar-2022	Initial approved SAP	N/A	N/A
Derivation of primary or secondary endpoints	11-Apr-2022	Lower visit window (Section 3.3.2) used for OCS dose derivation at Week 52 updated from "Visit 15 date + 2 days" to "Visit 14 + 2 days".	N/A	To provide correct information of the derivation.
Derivation of primary or secondary endpoints	11-Apr-2022	Clarification added that if the end date of the first exacerbation and the start date of the second exacerbation are less than 7 days, then it is counted as one exacerbation (Section 4.2.2.2).	Yes, CSP v2.0	To clarify rules of counting the number of exacerbations.
Derivation of primary or secondary endpoints	1-Dec-2022	Composite strategy updated to hypothetical strategy for handling intercurrent event of therapy initiation with another biologic for treatment of asthma (Section 1.1).	Yes, CSP v3.0	To correct the name of the strategy.
Derivation of primary or secondary endpoints	1-Dec-2022	The phrase "for treatment of asthma" added to "Initiate therapy with another biologic" (Section 1.1, Section 4.2 and Section 4.2.1.2).	Yes, CSP 3.0	To clarify that the intercurrent event is related to the initiation of other biologic for treatment of asthma.
Derivation of primary or secondary endpoints	1-Dec-2022	Wording of the derivation of time at risk updated to highlight the need of subtracting time of asthma exacerbations and 7 days following an exacerbation (Section 4.2.2.2).	N/A	To provide clarification of time at risk derivation.
Derivation of primary or secondary endpoints	9-Nov-2023	Corrected time at risk derivation and combined into one step (Section 4.2.2.2)	N/A	To correct the derivation details for time at risk.
Population definition	20-May-2022	Participants assigned to Currently or historically elevated EOS population have to be dosed with at least dose of tezepelumab (Section 3.2.3).	N/A	To provide clarification of definition of Currently or historically elevated EOS population.

General study level definitions	9-Nov-2023	"Visit 9 (Week 28)" removed from the planned treatment definition and details provided which data should be included in the primary database lock at Week 28. (Section 3.3.1.1)	N/A	To clarify the definition of planned treatment period and how it should be handled at the time of primary database lock.
General study level definitions	9-Nov-2023	Updated general baseline definition to emphasize that for efficacy variables baseline is the last assessment at or prior to the date of first dose of IP administration, while for safety variables time of the first dose of IP administration is additionally considered. (Section 3.3.1.2)	N/A	To provide clarity on the time of baseline assessment and time of first dose of IP administration in the baseline definition.
Data presentation	11-Apr-2022	Visit window (Section 3.3.2) for Week 64 provided.	N/A	To provide missing information.
Data presentation	20-May-2022	Information how to classify countries into regions has been provided (Section 4.1.1.1).	N/A	To provide details of regions' definition.
Data presentation	20-May-2022	Participants' recruitment, as well as disposition and disruption due to global/country situation summary tables are presented based on Full analysis set, and not on All participants set (Section 4.1.1.2).	N/A	To clarify analysis set used in selected summary tables.
Data presentation	20-May-2022	Added information that participants' disposition is also presented graphically (Section 4.1.1.2).	N/A	To clarify the participants' disposition should also be presented on the graph often used in external materials (manuscripts, posters, etc.).
Data presentation	20-May-2022	Reference added to CSP Appendix I showing derivation of medium/high ICS group based on total daily ICS dose (Section 4.1.8.2).	Yes, CSP v2.0	To give details of derivation of medium/high ICS group.
Data presentation	20-May-2022	Shift tables have been added showing the daily OCS dose at baseline vs. the final OCS dose at Week 28, and the final OCS dose at	N/A	Analysis added to support the interpretation of the primary objective.

		Week 28 vs. the final OCS dose at Week 52 (Section 4.2.1.4).		
Data presentation	20-May-2022	The relation between the percent change from baseline in daily OCS dose at Week 28 (Week 52) and continuous baseline biomarkers (EOS, FeNO, total IgE) is presented graphically using nonparametric approach (Section 4.2.7.4).	N/A	To better explore the relation between percent change from bassline baseline in daily OCS dose and biomarkers level at baseline.
Data presentation	20-May-2022	Table presenting cumulative SCS dose over time added (Section 4.2.21.4) .	N/A	Analysis added to support the interpretation of the endpoint of mean daily exposure of systemic corticosteroids.
Data presentation	20-May-2022	Specify that the mean cumulative SCS dose (mg) is presented on the graph with ± 1 standard error of the mean (Section 4.2.21.4).	N/A	To provide clarification on visual representation of the analysis results.
Data presentation	20-May-2022	The summary of number of dosing occasions added (Section 4.6.1.2).	N/A	To be aligned with data presentation across tezepelumab studies.
Data presentation	20-May-2022	AESIs are not presented on the overall AE summary tables. Information about intensity of AEs is listed and not summarised in the summary table (Section 4.6.2.2).	N/A	To be aligned with data presentation across tezepelumab studies.
Data presentation	1-Dec-2022	Details added of how the study population data is presented for Interim Analysis (Sections: 4.1.1.2, 4.1.4.2, 4.1.5.2, and 4.1.8.2).	N/A	To describe presentation of study population for the interim analysis.
Data presentation	1-Dec-2022	Additional sections regarding Interim Analysis added specifying derivation and presentation of efficacy endpoints (Sections 4.2.1.8 – 4.2.21.7).	N/A	To describe presentation of primary and secondary endpoints for the interim analysis.
Data presentation	1-Dec-2022	Clarification added that descriptive statistics for continuous secondary and exploratory endpoints are provided for both absolute	N/A	To clarify the presentation of continuous endpoints.

		values and changes from baseline (Sections: 4.2.8.4 – 4.2.21.7).		
Data presentation	1-Dec-2022	Adjusted incidence rate definition added to the AE Section 4.6.2.1. Description of AEs presentation updated in Section 4.6.2.2. In addition, details regarding presentation of AEs for Interim Analysis provided in Section 4.6.2.2.	N/A	To clarify the presentation of AEs.
Data presentation	1-Dec-2022	The presentation of clinically important abnormalities of laboratory data (blood samples) updated from summary table to listing (Section 4.6.3.2).		To clarify the presentation of laboratory data.
Data presentation	9-Nov-2023	Added three additional categories to the disposition summary: participants who completed 28 weeks of treatment, participants who discontinued treatment at or prior to Week 28 (and reasons), and participants who withdrew from study at or prior to Week 28 (including reasons). (Section 4.1.1.2)	N/A	To improve clarity for the primary analysis at Week 28.
Data presentation	9-Nov-2023	Additional subgroups added to align with CSR requirements. (Section 4.2.1.7)	N/A	To align with CSR requirements.
Data presentation	9-Nov-2023	Added clarification on the minimal subgroup size required to conduct the model-based analysis i.e., the subgroup has to consist of at least 10 participants to be included in the model. (Section 4.2.1.7)	N/A	To provide clarity on small subgroups handling in the statistical models.
Data presentation	9-Nov-2023	Added definition, derivation and presentation details for participants requiring repeated morning cortisol testing for whom ACTH test is not available. (Section 4.2.14)	N/A	To provide information regarding the two steps for Adrenal Insufficiency testing (for details see CSP Appendix M).
Data presentation	9-Nov-2023	Removed listings of pregnancy test results and clarified that the analysis of positive results is	N/A	To align with Tezepelumab program reporting.

		not within the scope of this SAP. (Sections 4.6.4.2 and 4.6.5.2)		
Other	20-May-2022	A statement "mixed model for repeated measures (MMRM)" was replaced with "model for repeated measures" (Section 4.2.7.4).	Yes, CSP v2.0	To highlight that no RANDOM statement is used in the model specification.
Other	1-Dec-2022	Change from baseline in AIRQ™ and proportions of AIRQ™ responders at Week 28 have been deleted from exploratory endpoints (Section 1.1).	Yes, CSP v3.0	To align with CSP v3.0
Other	1-Dec-2022	Asthma exacerbation definition has been updated (Section 1.1, Section 1.2).	Yes, CSP v3.0	To align with CSP v3.0 definition.
Other	1-Dec-2022	Study design description updated (Section 1.2), including information about alternative method to ACTH stimulation test.	Yes, CSP v3.0	To align with CSP v3.0
Other	1-Dec-2022	Section 2 updated to remove changes which have been incorporated in revised CSP since SAP v3.0.	Yes, CSP v3.0	Following revision to CSP v3.0
Other	1-Dec-2022	Interim analysis (IA) has been added (Section 3.1, Section 5). Statement added that IA does not impact the sample size of the study (Section 1.3).	Yes, CSP v3.0	To align with CSP v3.0

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D5180C00037 supporting the clinical study report (CSR).

The reader is referred to the clinical study protocol (CSP) and the electronic case report form (eCRF) for details of study conduct and data collection.

1.1 Study objectives

Table 1 Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary objectives	
To assess the ability of tezepelumab 210 mg subcutaneous (SC) to reduce the prescribed OCS dose (≤ 5 mg/day) without loss of asthma control[a] in adult participants with OCS-dependent asthma	Endpoints • Proportion of participants who discontinued OCS without loss of asthma control[a] at Week 28 and Week 52 • Proportion of participants who reduced daily prescribed maintenance OCS dose to ≤ 5 mg/day without loss of asthma control[a] at Week 28 and Week 52
	Population: Adult with OCS-dependent asthma requiring high-dose ICS plus a LABA with or without additional asthma controller and with at least 1 asthma exacerbation in the prior year who received at least one dose of tezepelumab
	Intercurrent events: • Treatment discontinuation, change in background therapy (other than OCS): All data are included in the analysis according to treatment policy estimand. • Initiate therapy with another biologic for treatment of asthma: hypothetical strategy; final dose for analysis is defined as last reported OCS dose received by participant with asthma stability verified, achieved prior to initiation of another biologic.

	Summary measures: Proportion of participants and corresponding 95% CI at Week 28 and Week 52
Secondary objectives	
To assess the ability of tezepelumab 210 mg SC to prevent asthma exacerbations in adult participants with OCS-dependent asthma while OCS dose reduction	• The AAER over 28 weeks and over 52 weeks • Rate of asthma exacerbation associated with hospitalisation or emergency room (ER) visit over 28 weeks and over 52 weeks • Rate of asthma exacerbation associated with hospitalisation over 28 weeks and over 52 weeks • Proportion of participants who did not experience an exacerbation over 28 weeks and over 52 weeks • Proportion of participants who did not experience an exacerbation associated with hospitalisation or ER visit over 28 weeks and 52 weeks • Proportion of participants who did not experience an exacerbation associated with hospitalisation over 28 weeks and over 52 weeks
To assess the ability of tezepelumab 210 mg SC to allow reduction of the prescribed OCS dose without loss of asthma control[a]	• Proportion of participants with ≥ 50% reduction from baseline in daily maintenance OCS dose at Week 28 and Week 52 • Categorised percent reduction from baseline in the daily maintenance OCS dose (categories: ≥ 90% to ≤ 100% reduction, ≥ 75% to < 90% reduction, ≥ 50% to < 75% reduction, > 0% to < 50% reduction, no change or any increase) at Week 28 and Week 52 • Absolute and percent change from baseline in daily maintenance OCS dose at Week 28 and Week 52
To assess the ability of tezepelumab to improve lung function	• Change from baseline in post-BD FEV_1 at Week 28 and Week 52

To assess the ability of tezepelumab to improve asthma control[a]	• Change from baseline in Asthma Control Questionnaire 6 (ACQ-6) at Week 28 and Week 52
To assess the ability of tezepelumab to improve asthma related quality of life	• Change from baseline in standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ[s]+12) total score at Week 28 and Week 52 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 28 and Week 52
Safety objective	
To describe the safety and tolerability of tezepelumab	• Serious adverse events (SAEs), discontinuation of investigational product due to an adverse event (DAEs), and adverse events of special interest (AESI)
Exploratory objectives	
To describe changes from baseline in biomarker levels	• Change from baseline in biomarker levels at Week 28 and Week 52
To assess the ability of tezepelumab 210 mg SC to allow reduction of the prescribed OCS dose without loss of asthma control[a]	• Time to 50% reduction of OCS dose at Week 28 and Week 52 • Time to 100% reduction of OCS dose at Week 28 and Week 52
To describe the occurrence of AI	• Proportion of participants with normal, partial, complete AI at Week 28 and Week 52
To assess the ability of tezepelumab to improve asthma control[a]	• Proportion of ACQ-6 responders at Week 28 and Week 52
To assess the ability of tezepelumab to improve asthma related quality of life	• Proportion of AQLQ(s)+12 responders at Week 28 and Week 52 Proportion of SGRQ responders at Week 28 and Week 52
To describe the ability of tezepelumab to improve Asthma Impairment and Risk Questionnaire (AIRQ™)	• Change from baseline in AIRQ at Week 52 • Proportions of AIRQ responders at Week 52

To describe the ability of tezepelumab to improve Sino-nasal Outcome Test (SNOT-22)	• Change from baseline in Sino-nasal Outcome Test (SNOT-22) at Week 28 and Week 52 • Proportion of SNOT-22 responders at Week 28 and Week 52
To describe participant satisfaction with change in daily OCS use	• Change from baseline in Participant Perception of OCS (PPOCS) score at Week 28 and Week 52
To evaluate the ability of tezepelumab to reduce exposure to SCS	• Mean daily exposure of systemic corticosteroids (mg/day) taken for asthma reasons over 28 and 52 weeks

[a] Loss of asthma control is defined as asthma worsening or exacerbation. Asthma worsening is defined by an increase of ACQ-6 score ≥ 0.5 from baseline. Asthma exacerbation is defined by worsening of asthma symptoms that leads to temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days (a single depo-injectable dose of corticosteroids being considered equivalent to a 3-day bolus/burst of systemic corticosteroids), and/or an ER or urgent care visit requiring systemic corticosteroid, and/or inpatient hospitalisation, both due to asthma.
[b] The AIRQ questionnaire is not assessed at Week 28 and the objective is analysed at Week 52 only (see Section 2).

1.2 Study design

This is a phase 3b, single-arm, multicentre study in adult participants with severe asthma on high-dose ICS plus LABA and long-term OCS therapy. Participants may be treated with or without additional asthma controller(s). Each participant must have been receiving an average daily OCS dose equivalent to ≥ 5 mg of prednisone/prednisolone for the last 3 months before study entry.

Approximately 300 participants will enter the induction phase. The distribution of participants across the range of screening blood EOS levels are controlled by ensuring that approximately the following ratios are met:

- 80% of participants with blood EOS count at screening ≥ 150 cells/µL
- 10% of participants with blood EOS count at screening < 150 cells/µL and documented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1
- 10% of participants with blood EOS count at screening < 150 cells/µL without documented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1 (ie, participants with documented EOS < 300 cells/µL over the last 12 months prior to Visit 1, or undocumented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1 or unknown EOS counts within 12 months prior to Visit 1).

The study aims at evaluating the efficacy and safety of reducing OCS use after initiation of a 210 mg dose of SC tezepelumab Q4W.

The total duration of the study for each participant is approximately 68 weeks.

Study is divided in 4 periods: screening, induction phase, OCS reduction and maintenance phase, and follow-up as described below and summarized in the Figure 1.

1. **Screening – From Week -4 to Week 0 (up to 4 weeks):** Eligibility criteria checked at Visit 1. At Visit 1, participants continue with or be switched to prednisone/prednisolone. Participants who are taking an alternative systemic steroid and not taking prednisone/prednisolone as their OCS treatment are switched to a bioequivalent dose of prednisone/prednisolone (see CSP appendix D). In participants who switched to prednisone/prednisolone, dose has to remain stable for at least 2 weeks before Week 0.
2. **Induction phase – From Week 0 to 4:** After confirmation of eligibility criteria, participants start receiving tezepelumab treatment at Visit 2/Week 0 and should remain stable on their baseline OCS dose during this phase.
3. **Oral corticosteroid reduction and maintenance phase – From Week 4 to Week 52:** Site visits occur Q4W. Participants reduce their dosage of OCS according to the schema defined in the CSP Table 7 for each baseline OCS dose until they reach the lowest stable OCS dose or until Week 48. The first OCS dose reduction may occur at Visit 3. OCS dose reduction may occur remotely if the scheduled dose reduction does not coincide with a site visit.

   Participants are considered as having reached the lowest stable dose when they have discontinued OCS or no further OCS reduction is possible because of loss of asthma control and/or evidence of AI (as confirmed by morning cortisol test or adrenocorticotropic hormone [ACTH] stimulation test).

   Once they reach the lowest stable dose, participants are considered in maintenance period. From Week 48 to Week 52, all participants remain on their stable daily OCS dose, except if an asthma deterioration or exacerbation occurs. No further down-titration are allowed from Week 48 onwards.

   The evaluation of the HPA axis integrity starts for all participants who have been on 5 mg/day OCS. A screening method with morning serum cortisol is done to evaluate whether the participant has normal cortisol levels or complete AI. Cortisol levels from the morning cortisol test below normal range and above the complete AI range are considered ‘indeterminate’ and will require additional testing (ACTH stimulation test or alternative method). Further details are provided in the CSP Section 8.2.1 and CSP Appendix M).

   At each visit, in addition to the participant’s asthma symptoms, investigators use the participant’s weekly ACQ-6 scores (completed by the participant at home by means of a handheld electronic participant-reported outcome device [ePRO]), and

further reduce the OCS dose unless asthma control is lost (deterioration or exacerbation as described below) or AI prevents further dose reduction.

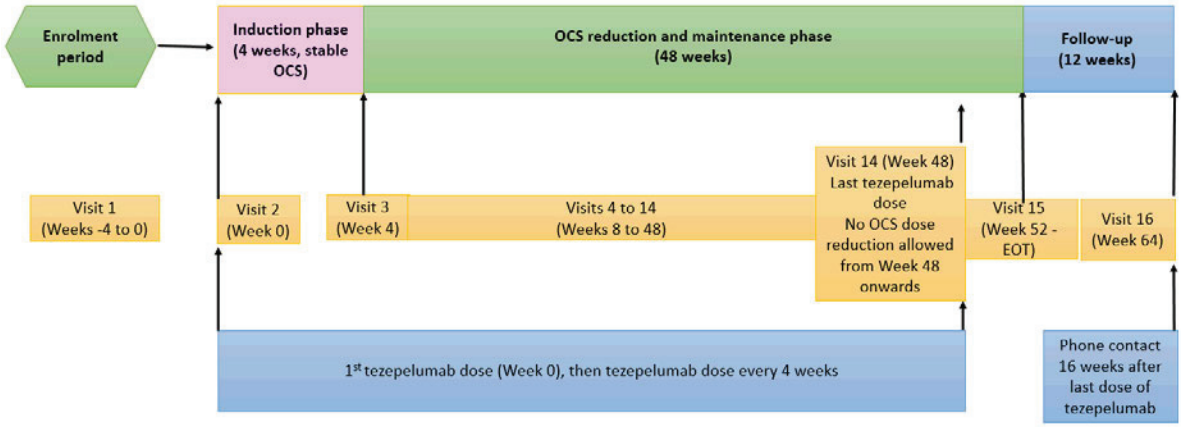
Asthma deterioration is defined by an increase of ACQ-6 score ≥ 0.5 from baseline. Asthma exacerbation is defined by worsening of asthma symptoms that leads to:

- A temporary bolus/burst of systemic corticosteroids (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 systemic corticosteroids.
- Or, an ER or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or in an urgent care centre) due to asthma that required systemic corticosteroids (as per the above).
- Or, an in-patient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma.

After recovery from the first exacerbation or asthma deterioration, the participant is allowed to proceed with another attempt to reduce OCS dose; however, this must follow a lower speed of OCS down-titration. In case of a second exacerbation or asthma deterioration, no further OCS dose reduction is allowed, and the participant continues the same OCS dose or return to a one-step higher dose level (or more as considered necessary by the investigator). The new OCS dose established after a second asthma exacerbation or deterioration is maintained until Week 52. Further details are provided in the CSP.

4. **Follow-up (Week 64):** A follow-up contact (phone call) is scheduled at Week 64 or 16 weeks (± 5 days) after the last dose of tezepelumab.

Figure 1 Study Design flow chart



All participants who prematurely discontinue tezepelumab or discontinue from the study should return to the study site and complete the procedures described for the premature IPD visit within 4 weeks (± 7 days) after the last dose of tezepelumab. In addition, participants who prematurely discontinue tezepelumab are encouraged to remain in the study and complete all subsequent scheduled study visits, procedures, and assessments through study completion (more details in CSP Section 7.1).

1.3 Sample size justification

The sample size for this study is based on the ability to provide sufficient precision in point estimates, both in the Full Analysis Set (FAS) and subsets for statistical analysis.

The primary outcomes variables, the proportion of participants who have discontinued OCS without loss of asthma control and the proportion of participants who reduced OCS dose to ≤ 5 mg/day without loss of asthma control. For the sample size estimation, a success rate of 50% is assumed. Estimate precision is expressed in a two-sided 95% CI distance from the point estimate of a 50% success rate to confidence limit for a total of approximately 300 participants. Calculations were conducted using the exact Clopper-Pearson CI formula for a single proportion in R v.4.0.1 (function *binom.test()* from *stats* package).

A total sample size of approximately 300 participants entering the induction phase was expected to provide 95% CIs for a single proportion extending approximately 5.8% from the point estimate of a 50% success rate. Estimates of the 95% CI of a > 50% success rate are incrementally smaller, as is shown in Table 2.

Table 2 Expected Distance Between Observed Proportion and Confidence Limit (Clopper-Pearson 95% CI Width)

Proportion of participants	Sample size					
	50	**100**	**150**	**200**	**250**	**300**
50	± 14.5	± 10.25	± 8.3	± 7.1	± 6.4	± 5.8
60	-14.8 +13.6	-10.3 +9.7	-8.3 +7.9	-7.1 +6.8	-6.4 +6.1	-5.8 +5.6
70	-14.6 +12.1	-10.0 +8.8	-8.0 +7.2	-6.9 +6.3	-6.1 +5.6	-5.5 +5.1
80	-13.7 +10.0	-9.2 +7.3	-7.3 +6.1	-6.2 +5.3	-5.5 +4.8	-5.0 +4.4

The table also shows that the 95% CIs for subpopulation analyses as small as 50 are < 15% for proportions between 50% and 80%.

Note: The planned interim analysis does not impact the sample size calculation.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

No difference with the most recent version of the CSP.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

There are 2 database locks (DBLs). The primary DBL carried out after approximately 300 participants completed 28 weeks. All data available at that time is part of the DBL and is analysed with the main focus on estimates of a subset of the pre-planned analysis outputs at Week 28. The final DBL conducted once the last participant completed the safety follow-up visit (Week 64) with the main focus on estimates on Week 52 (end of treatment [EOT]).

An interim analysis (IA) may also be performed as described in Section 5.

3.2 Analysis Populations

3.2.1 All Participants Analysis Set

Comprises all participants screened for the study and used for reporting of disposition and screening failures.

3.2.2 Full Analysis Set

Includes all enrolled participants who received at least one dose of tezepelumab, irrespective of their protocol adherence and continued participation in the study. Participants are analysed irrespective of whether they prematurely discontinue, according to the intent-to-treat principle. Participants who withdraw from the study are included up to the date of their study termination.

All efficacy, demographics, baseline characteristics, and safety analyses are performed using the FAS.

3.2.3 Currently or Historically Elevated EOS Population

Includes participants who received at least one dose of tezepelumab and with peripheral blood EOS count of ≥ 150 cells/μL assessed by central laboratory at Visit 1 or documented EOS count of ≥ 300 cells/μL in the past 12 months. Participants are analysed irrespective of whether they prematurely discontinue, according to the intent-to-treat principle. Participants who withdraw from the study are included up to the date of their study termination.

Primary efficacy analyses, key demographics and baseline characteristics are also presented using the currently or historically elevated EOS population in addition to the FAS as described in Section 3.2.2.

3.3 General Considerations

In general, continuous endpoints are summarised using the mean, the standard deviation, median, minimum value, and maximum value, and the categorical endpoints are summarised using frequency counts and percentages, as well as a two-sided 95% CI for proportions computed using exact Clopper-Pearson method. Time to event data is presented graphically using Kaplan Meyer curve.

Absolute change from baseline is defined as *(post-baseline value – baseline value)*. The percent change from baseline is defined as *{(post-baseline value – baseline value)/baseline value)}*100*. Baseline calculations are defined in the Section 3.3.1.2.

For participants' proportion calculation, the denominator is the number of participants in the Full Analysis Set defined in Section 4.1.2 unless otherwise stated.

No imputation performed beyond the approach defined for outcome measures. Imputation for partial date is detailed in the Appendix A.

Unless specified otherwise, the daily maintenance OCS dose, including the daily OCS at baseline (Section 3.3.1.2) and the final daily OCS dose (Section 4.2.1.2), is defined based on the prescribed maintenance dose of OCS, expressed as a dose per day, at the time of the relevant visit. If a participant is on a fixed daily dose, then the OCS dose is defined as that prescribed dose. If the participant is on every other day regimen (or different doses every other day), then the OCS dose is defined as the average amount prescribed to be taken each day. For example, should a participant be on a 10 mg every other day regimen of OCS, their OCS dose is defined as 5 mg.

Maintenance dose of OCS is collected on the ECSYSCRT eCRF page with a therapy reason of *"Asthma maintenance dose"*, *"Titration, due to asthma"*, *"AI based on cortisol test"*, *"Signs/symptoms of AI"* and *"Adrenal crisis"*. If the maintenance OCS doses with more than one therapy reasons (including only those mentioned earlier) are prescribed on the same day (e.g., *"Asthma maintenance dose"* and in addition *"Signs/symptoms of AI"*), then the sum of the doses are calculated.

Note that the prescribed OCS dose with therapy reason of "Asthma exacerbation per protocol" or "Worsening of asthma, without exacerbation" is not included in the daily OCS dose calculation. In case of overlapping OCS doses taken for asthma worsening or exacerbation with maintenance doses of OCS, the latter one is excluded from the daily OCS dose calculation.

The statistical analyses for this study are conducted using SAS® v9.4 or latest version in a secure and validated area.

3.3.1 General Study Level Definitions

3.3.1.1 Study period definition

Efficacy analyses are based on planned treatment period, unless otherwise specified. Safety analyses are based on-treatment and/or on-study period.

- Planned treatment period: starts on the date of first dose of IP and ends on the date of the Visit 15 (Week 52) visit or earlier study withdrawal date.
- On-treatment period: starts on date of first dose of IP and ends on earliest(date of last dose of IP + 33 days, date of death, 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.
- On-study period (planned treatment period and follow-up): starts on the date of first dose of IP and ends on the study completion or withdrawal date.

For analysis performed at primary database lock, the planned treatment period is understood to include all data recorded starting on the date of first dose of IP up until the date of the data cut-off for the primary database lock (details regarding the DCO date and data cleaning can be found in Data Cleaning Requirements for Primary Analysis Lock Plan).

3.3.1.2 Baseline definition

In general, the last non-missing measurement on or prior to the date of the first dose of IP is served as the baseline measurement of efficacy analyses. If there is no value at or prior to the date of the first dose of IP, then the baseline value is not imputed and is set to missing.

In general, the last non-missing measurement at or prior to the date and time of the first dose of IP is served as the baseline measurement of safety analyses. If there is no value at or prior to the date and time of the first dose of IP, then the baseline value is not imputed and is set to missing.

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

The baseline OCS dose is the prescribed OCS doses prior to the date of the first dose of IP and derived following rules described in Section 3.3.

3.3.2 Visit Window

For summaries and/or analyses presented by time points, visit window need to be defined for classifying records. The visit window is derived from the assessment date relative to the reference start date. This approach allows appropriate classification of visits which may

have occurred significantly earlier or later than the protocol assessment schedule, as well as the use of data captured at visits which have no fixed timing, and the handling of data captured at visits for which the database label is incorrect and unresolvable.

Nominal database visit numbers are not used in any summary or analysis by visit. The relative day is defined as (Date of assessment – Date of first dose of IP) + 1.

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 replace the missing value at the scheduled visit.

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

- The non-missing value closest to the target day is selected for analysis at that visit
- If two non-missing values are the same distance from the target day, the earlier of the two values are selected for analysis at that visit
- If two non-missing values are recorded on the same day and have a different assessment time associated with both of them, the value with the earliest assessment time is selected for analysis at that visit.
- If two non-missing values (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 of them, the average of the two values are selected for analysis at that visit. For categorical variables in this situation, the worst case is used.

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.

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

Table 3 summarises the visit windows to be used. "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.

The 4-weekly visit window approach is replaced by a weekly based approach for ACQ-6 measured weekly. For Week 1, the window is [2; 11] and then for each week, the window is defined as (Target day for Week X – 3; Target day for Week X + 3), where Target day for Week X = (Week number * 7) + 1. For example: Target day for Week 10 is 71 (i.e., 10*7+1) and the visit window is (68 – 74).

Visit windows presented in Table 3 does not apply for calculation of daily OCS dose at each timepoint. The OCS dose at each visit is based on actual visit dates to account for changes in OCS dose at scheduled visit. The visit window at Week X is calculated as [Visit(X-1) date + 2 days; Visit(X) date + 1 day]. For Week 52, the visit window is [Visit 14 date + 2 days; Visit 15 date].

Table 3. Adjusted analysis Visit Windowing

Visit	**Time Point**	**Target Day**	**4-weekly Visit Window**	**Sparse Visit Window** *(Sparse CSP schedule)*		
				AQLQ	SGRQ/ PPOCS/ SNOT-22	AIRQ
Visit 2	Week 0	1	NA	NA	NA	NA
Visit 3	Week 4	29	2 - 42	2-56	-	-
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	-	-	-
Visit 9	Week 28	197	183 - 210	169-224	169-224	-
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
Visit 16	Week 64	449	≥379	-	-	-

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. Listings of data includes all scheduled and unscheduled visits.

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 tested in this study, and no multiplicity adjustment applied in the statistical analysis.

3.3.5 Handling of Protocol Deviations in Study Analysis

Participants who do not meet eligibility criteria but enrolled is analysed according to FAS as described in Section 3.2. There is no intention to perform a per-protocol analysis in this study. Only important protocol deviations are listed and tabulated in the Clinical Study Report (CSR), and only participants in FAS (not screening failures). Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

Important protocol deviations are defined prior to first participants enrolled. Participants are not excluded from any analysis sets on the basis of any important protocol deviations. The list of important protocol deviations is documented prior to primary DBL (Week 28) and final DBL and includes but are not limited to the following categories:

- Informed Consent (version, process, signature/date, presence/absence, other)
- Study Conduct/Procedures (inclusion/exclusion criteria, study assessment study restrictions/withdrawal criteria, sample processing/storage, sample shipping, other)
- Investigational Product (supply, dispensing/accountability, handling/storage/retention, dose formulation/dose administration, sample collection, other)
- Safety (recording, reporting/follow-up, other)
- GCP violation

The process for identification and assessment is detailed in a separate Protocol deviation plan.

4 STATISTICAL ANALYSIS

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

4.1 Study Population

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Disposition information and completion status are directly obtained from electronic case report form (eCRF). Regions are defined as follows:

- Central/Eastern Europe: Bulgaria, Latvia, and Poland
- Western Europe: Belgium, Germany, France, Spain, and United Kingdom
- South America: Argentina and Mexico
- North America: Puerto Rico and United States of America.

4.1.1.2 Presentation

Participants' disposition is summarised and presented graphically on the All participants analysis set. The number of enrolled participants, number of participants who received IP, did not receive IP (and reasons), completed treatment, discontinued treatment (and reasons), completed 28 weeks of treatment, discontinued treatment at or prior to Week 28 (and reasons), completed study (participants who completed IP and study, and participants who discontinued IP but completed study assessments), withdrew from study (including reasons), and withdrew from study at or prior to Week 28 (including reasons). The number and percentage of participants, who discontinued IP, but remained in the study is presented by option of follow up (i.e., 1: Return for all regular clinic visits and perform all scheduled assessments; 2: Monthly telephone follow-up with eDiary completion; 3: Contact at Week 52).

Participant's disposition variables, except for the completed treatment and completed study, are also presented for the interim analysis. The summary is presented on the All participants analysis set.

The number of subjects who discontinued treatment or withdrew from study due to global/country situation together with reasons is presented based on Full Analysis Set. The number and percentage of participants with at least one missed visit, visits contact mode affected by global/country situation is presented. A listing of all participants impacted by global/country situation is produced with details of changed or missed visits.

Participant recruitment by region, country and centre is summarised based on Full Analysis Set.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Definitions of analysis sets are provided in Section 3.2.

4.1.2.2 Presentation

The number and percentages of participants are presented for each analysis set.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

The definition of protocol deviations and derivations are described in Section 3.3.5.

4.1.3.2 Presentation

Protocol deviations are summarised using FAS. The number and percentage of participants with at least one important protocol deviation as well as each important protocol deviation is described.

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 3.3.5. 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. A listing of all global/country situation related protocol deviations (important and non-important PDs) is provided.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

All demography information can be directly retrieved from the eCRF. Age is directly collected in the eCRF as well as sex, ethnicity and race. In addition, participants are classified based on age group (≥18 to <65 years, ≥65 years).

4.1.4.2 Presentation

Demographics are summarised using frequency counts and percentages (for categorical variables) and n, mean, standard deviation, median, minimum and maximum (for age variable) using the FAS and the currently or historically elevated EOS populations. Demographics are also summarised for the interim analysis on the FAS.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Various baseline characteristics are summarised in FAS and the currently or historically elevated EOS populations. These include height (cm), weight (kg), BMI (kg/m^2) calculated

as weight (kg) divided by (height (m))^2, BMI categorised (<25 kg/m^2; 25 to <30 kg/m^2; ≥30 kg/m^2), post-BD FEV1 (L), ACQ-6 score, daily OCS dose (mg), daily OCS dose categorised as in Section 4.2.1.7, biomarker levels (FeNO, eosinophils and IgE), biomarker levels categorised as in Section 4.2.1.7, and allergic status defined as follows:

- Baseline (Any) specific IgE status (FEIA): Any FEIA positive, All FEIA negative, Unknown FEIA
  - "Any FEIA positive" requires 1 or more specific IgE panels using fluorescent enzyme immunoassay (FEIA) to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 11 panels to be available.
  - "All FEIA negative" requires all 11 specific IgE panels to be negative.
  - If there are fewer than 11 panels with data available and none of these is positive, then IgE status is considered "Unknown FEIA".
  - Positive is defined as a value ≥0.35 kU/L.
- Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial FEIA negative, Unknown perennial FEIA
  - "Any perennial FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 7 panels to be available.
  - "All perennial FEIA negative" requires all 7 specific IgE panels to be negative.
  - If there are fewer than 7 panels with data available and none of these is positive, then IgE status is considered "Unknown perennial FEIA".
  - Positive is defined as a value ≥0.35 kU/L.
  - The 7 panels include: American Cockroach, Cat Dander, D. farina, D. pteronyssinus, Dog Dander, German Cockroach, Mould Mix.
- Baseline specific IgE status (FEIA): Any seasonal FEIA positive, All seasonal FEIA negative, Unknown seasonal FEIA
  - "Any seasonal FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 4 panels to be available.
  - "All seasonal FEIA negative" requires all 4 specific IgE panels to be negative.

- If there are fewer than 4 panels with data available and none of these is positive, then IgE status is considered "Unknown seasonal FEIA".

- Positive is defined as a value ≥0.35 kU/L.

- The 4 panels include: Grass Mix Pollen, Silver Birch Pollen, Weed Mix Pollen, Japanese Cedar.

4.1.5.2 Presentation

Baseline characteristics are summarised in a similar manner to that described for baseline demographics (see Section 4.1.4.2). Baseline characteristics are also summarised for the interim analysis on the FAS.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Baseline disease characteristics includes the asthma duration, age at onset of asthma, GINA classification (mild, moderate, severe), asthma history characteristics (allergen/aspirin/exercise /other asthma trigger, previous admission to ICU, need of mechanical ventilation). Number of asthma exacerbations in the previous 12 months, number of asthma exacerbations requiring hospitalisations in the previous 12 months, any asthma exacerbation required hospitalisation, asthma exacerbation medications are also described.

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

4.1.6.2 Presentation

Disease characteristics are summarised on the FAS in a similar manner to that described for baseline demographics (see Section 4.1.4.2).

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history information can be directly obtained from the eCRF. In case of a partial diagnosis date, if both the month and the year are available then the 1st is imputed for the day. If only the year is available, 1st January is imputed.

4.1.7.2 Presentation

Medical history is summarised by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by the Medical Dictionary for Regulatory Activities (MedDRA) dictionary using frequency counts and percentage of participants in the FAS. For each PT, the number and percentage of participants reporting at least one occurrence are presented, i.e., multiple occurrences of a medical history for a participant are counted only once.

Specific surgical histories such as bronchial thermoplasty in the last 12 months are summarised by SOC and PT, separately from medical history.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Medications taken by any participant at any time during the study are coded using the ATC classification system within the WHO Drug Dictionary. Medications are categorised for analysis according to their onset and end dates.

Prior medications are defined as those which stopped before first dose of IP. Concomitant medications are defined as those which either started or continued after first dose of IP. Concomitant medications are also defined on-treatment and off-treatment period as follows:

On-treatment period concomitant medication:

- end date ≥ date of first dose of IP and start date ≤ earliest(date of last dose of IP + 33 days; date of death, date of study withdrawal), or
- end date ongoing and start date ≤ earliest(date of last dose of IP + 33 days, date of death, date of study withdrawal)

Off-treatment period concomitant medication:

- start date > date of last dose of IP + 33 days

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

Disallowed medications include medications defined as prohibited accordinsg to CSP Section 6.5. Disallowed medications include prohibited and restricted drugs; restricted drugs are considered a disallowed medication depending on timing of use, or if there are changes in dose and regimen during the study as defined in the CSP. They will be defined following a physician review (prior to primary database lock) of the unique combinations of ATC code classifications and generic terms captured.

The handling of partial/missing dates for prior/concomitant medications is detailed in Appendix A.

4.1.8.2 Presentation

The number and percentage of participants receiving each medication (by generic term within ATC code) is 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 4.1.8.1. Similar tables are presented for subjects who took disallowed concomitant medications.

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

Table for maintenance medications (started prior to the first day of IP) are produced displaying the baseline total daily dose categories (medium/high) of ICS medications (CSP Appendix I). The number of subjects using other maintenance asthma medications at baseline is also summarised. This summary is also presented for the interim analysis on the FAS.

Percentages are calculated relative to the number of subjects in the FAS.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Treatment compliance is calculated as follows:

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

To allow a participant who discontinues IP early in the compliance calculation, the total expected dosing occasion is calculated as the number of expected dosing occasions up to and including the last available dosing occasion for that participant.

4.1.9.2 Presentation

Study treatment compliance is summarised using the FAS.

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

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary and other endpoints. No sensitivity analysis is planned for this study. A supportive analysis is planned for primary endpoints.

An interim analysis may be performed as detailed in Section 5 with approximatively 50 participants completing V4 before the data cut-off. As the study duration for those participants is shorten than the primary analysis evaluation at Week 28, the derivation and/or presentation of OCS-related endpoints have to be adjusted. No changes to the

strategies of handling intercurrent events were introduced. Details are provided in specific sections of the SAP.

Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary objective: To assess the ability of tezepelumab 210 mg subcutaneous (SC) to reduce the prescribed OCS dose (≤ 5 mg/day) without loss of asthma control[a] in adult participants with OCS-dependent asthma				
Proportion of participants who discontinued OCS without loss of asthma control[a] at Week 28 and Week 52	FAS	- Treatment discontinuation, change in background therapy[b] (other than OCS): all data included in the analysis - Initiation of therapy with another biologic for treatment of asthma: final dose for analysis is defined as last reported OCS dose received by participant with asthma stability verified, achieved prior to initiation of another biologic.	Proportion of participants with 95% CI	4.2.1
Proportion of participants who reduced daily prescribed maintenance OCS dose to ≤ 5 mg/day without loss of asthma control[a] at Week 28 and Week 52				
Secondary objective: To assess the ability of tezepelumab 210 mg SC to prevent asthma exacerbations in adult participants with OCS-dependent asthma while OCS dose reduction				
The AAER over 28 weeks and over 52 weeks	FAS	- Treatment discontinuation, change in background therapy[b] (other than OCS): all data included in the analysis - Initiation of therapy with another biologic for treatment of asthma: only data collected up until the initiation of the other biologic treatment is included in the analysis.	AAER with 95% CI	4.2.1.8
Rate of asthma exacerbation associated with hospitalisation or emergency room (ER) visit over 28 weeks and over 52 weeks				4.2.3
Rate of asthma exacerbation associated with hospitalisation over 28 weeks and over 52 weeks				
Proportion of participants who did not experience an exacerbation over 28 weeks and over 52 weeks			Proportion of participants with 95% CI	4.2.4
Proportion of participants who did not experience an exacerbation associated with hospitalisation or ER visit over 28 weeks and 52 weeks				
Proportion of participants who did not experience an exacerbation associated with hospitalisation over 28 weeks and over 52 weeks				

Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary objective: To assess the ability of tezepelumab 210 mg SC to allow reduction of the prescribed OCS dose without loss of asthma control[a]				
Proportion of participants with ≥ 50% reduction from baseline in daily maintenance OCS dose at Week 28 and Week 52	FAS	Same intercurrent event strategies as for primary objective.	Proportion of participants with 95% CI	4.2.5
Categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 and Week 52				4.2.6
Absolute and percent change from baseline in daily maintenance OCS dose at Week 28 and Week 52		Same intercurrent event strategies as described for secondary objective related to exacerbation.	Least Square (LS) mean with 95% CI	4.2.7
Secondary objective: To assess the ability of tezepelumab to improve lung function				
Change from baseline in post-BD FEV_1 at Week 28 and Week 52	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	LS mean with 95% CI	4.2.8
Secondary objective: To assess the ability of tezepelumab to improve asthma control[a]				
Change from baseline in Asthma Control Questionnaire 6 (ACQ-6) at Week 28 and Week 52	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	LS mean with 95% CI	4.2.9
Secondary objective: To assess the ability of tezepelumab to improve asthma related quality of life				
Change from baseline in standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ[s]+12) total score at Week 28 and Week 52	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	LS mean with 95% CI	4.2.10
Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 28 and Week 52				4.2.11

Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Exploratory objective: To describe changes from baseline in biomarker levels				
Change from baseline in biomarker levels at Week 28 and Week 52	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	Unadjusted mean and standard deviation (SD)	4.2.12
Exploratory objective: To assess the ability of tezepelumab 210 mg SC to allow reduction of the prescribed OCS dose without loss of asthma control[a]				
Time to 50% reduction of OCS dose at Week 28 and Week 52	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	Kaplan-Meier estimates	4.2.13
Time to 100% reduction of OCS dose at Week 28 and Week 52				
Exploratory objective: To describe the occurrence of AI				
Proportion of participants with normal, partial, complete AI at Week 28 and Week 52	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	Proportion of participants with 95% CI	4.2.14
Exploratory objective: To assess the ability of tezepelumab to improve asthma control[a]				
Proportion of ACQ-6 responders at Week 28 and Week 52	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	Proportion of participants with 95% CI	4.2.15
Exploratory objective: To assess the ability of tezepelumab to improve asthma related quality of life				
Proportion of AQLQ(s)+12 responders at Week 28 and Week 52	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	Proportion of participants with 95% CI	4.2.16
Proportion of SGRQ responders at Week 28 and Week 52				4.2.17

Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Exploratory objective: To describe the ability of tezepelumab to improve Asthma Impairment and Risk Questionnaire (AIRQ)				
Change from baseline in AIRQ at Week 52	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	Unadjusted mean and SD	4.2.18
Proportions of AIRQ responders at Week 52			Proportion of participants with 95% CI	
Exploratory objective: To describe the ability of tezepelumab to improve Sino-nasal Outcome Test (SNOT-22)				
Change from baseline in Sino-nasal Outcome Test (SNOT-22) at Week 28 and Week 52	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	Unadjusted mean and SD	4.2.19
Proportion of SNOT-22 responders at Week 28 and Week 52			Proportion of participants with 95% CI	
Exploratory objective: To describe participant satisfaction with change in daily OCS use				
Change from baseline in Participant Perception of OCS (PPOCS) score at Week 28 and Week 52	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	Proportion of participants with 95% CI	4.2.20
Exploratory objective: To evaluate the ability of tezepelumab to reduce exposure to SCS				
Mean daily exposure of systemic corticosteroids (mg/day) taken for asthma reasons over 28 and 52 weeks	FAS	Same intercurrent event strategies as described for secondary objective related to exacerbation.	Unadjusted mean and SD	4.2.21
Safety objective: To describe the safety and tolerability of tezepelumab				
Serious adverse events (SAEs), AE leading to discontinuation of IP (DAEs), and adverse events of special interest (AESI)	FAS	All data included in the analysis regardless of treatment discontinuation, change in background therapy[b], or initiation of therapy with another biologic for treatment of asthma	Proportion of participants	4.6.2

[a] Loss of asthma control is defined as asthma worsening or exacerbation. Asthma worsening is defined by an increase of ACQ-6 score ≥ 0.5 from baseline

[b] Background therapies are collected within the CM eCRF form with Therapy reason "Disease under study".

4.2.1 Primary Endpoint - Proportion of participants who discontinue OCS, reduce OCS dose to ≤ 5 mg/day without loss of asthma control

4.2.1.1 Definition

The following primary endpoints are designed to support the primary objective of the study:

- Proportion of participants who discontinue OCS without loss of asthma control
- Proportion of participants who reduce OCS dose to ≤ 5 mg/day without loss of asthma control

Both proportions are assessed at Week 28 and at Week 52.

4.2.1.2 Derivations

The baseline OCS is defined in Section 3.3.1.2. The final OCS dose at Week 28 (Visit 9) or at Week 52 (Visit 15) is defined as in Section 3.3 and Table 4. Strategies of handling intercurrent events are presented in Section 4.2.

Table 4 Final daily maintenance OCS derivation

Situation	Final daily maintenance OCS dose
Initiation of therapy with another biologic for treatment of asthma	Last reported OCS dose[a] received by participant with asthma stability verified[b] prior to initiation of another biologic for treatment of asthma.
Premature withdrawal from the study	Last reported OCS dose[a] received by participant with asthma stability verified[b] at the time of study withdrawal.
Any other situation	Last reported OCS dose[a] received by participant with asthma stability verified[b]

[a] daily OCS dose is based on information collected in ECSYSCRT eCRF.

[b] Asthma stability is defined as no change in OCS dose for at least 2 consecutive weeks.

4.2.1.3 Handling of Dropouts and Missing Data

No data imputation for the primary endpoint.

4.2.1.4 Primary Analysis of Primary Endpoint

Shit tables are provided showing the daily OCS dose at baseline versus the final OCS dose at Week 28 and the final OCS dose at Week 28 versus the final OCS dose at Week 52.

Each primary endpoint is summarised by number and proportion (with 95% CI) of participants. The 95% CIs for each proportion are calculated using the Clopper-Pearson exact method on the FAS and the currently or historically elevated EOS population.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

No sensitivity analysis.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

The number and proportion (with 95% CI), as described in Section 4.2.1.4, is repeated using on-treatment data only, where the definition of on-treatment is given in Section 3.3.1.1. The final daily OCS dose for a participant withdrawing from the study or prematurely discontinuing IP (regardless of chosen option) is the last reported OCS dose received by the participant when asthma stability was verified, at the time of IP discontinuation, as described in Table 4 in Section 4.2.1.2. The derivation of the final daily OCS dose for any other participant is following the rules described in Table 4.

The analysis is performed based on both FAS and the currently or historically elevated EOS population.

4.2.1.7 Subgroup Analyses

The number and proportion with 95CI%, as described in Section 4.2.1.4, is also presented by the following pre-specified subgroups for both primary (Week 28) and final (Week 52) analysis:

- Eosinophils (EOS) at baseline group: < 300/µL, ≥ 300/µL
- Eosinophils (EOS) at baseline group: < 150/µL, ≥ 150/µL
- Eosinophils (EOS) at baseline group: <150, >=150 to <300, >=300
- Eosinophils (EOS) at screening group: <150 with documented high EOS, <150/µL without documented high EOS, >=150/µL
- Baseline FeNO group: < 25 ppb, ≥ 25 ppb
- Baseline (Any) specific IgE status (FEIA): Any FEIA positive, All FEIA negative, Unknown FEIA (see Section 4.1.5.1)
- Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial FEIA negative, Unknown perennial FEIA (see Section 4.1.5.1)
- Baseline seasonal specific IgE status (FEIA): Any seasonal FEIA positive, All seasonal FEIA negative, Unknown seasonal FEIA (see Section 4.1.5.1)
- Eosinophils (EOS) at baseline and baseline perennial specific IgE status (FEIA):
    - EOS < 150/µL and with any perennial FEIA positive
    - EOS ≥ 150/µL to < 300/µL and with any perennial FEIA positive
    - EOS ≥ 300/µL and with any perennial FEIA positive
    - EOS < 150/µL and with all perennial FEIA negative
    - EOS ≥ 150/µL to < 300/µL and with all perennial FEIA negative
    - EOS ≥ 300/µL and with all perennial FEIA negative
- Daily OCS dose at baseline: (≤10 mg versus >10 mg prednisone or prednisolone)
- Regions: Central/Eastern Europe (low availability of biologics), Western Europe (high availability of biologics), South America, North America (see Section 4.1.1.1)

- Therapy reason for SCS use related to AI: Yes (includes the following therapy reasons: AI based on cortisol test, Signs/symptoms of AI, Adrenal Crisis), No (all remaining therapy reasons)
- Access to ACTH Test (ACTH is not available in Poland, Bulgaria and Latvia, ACTH available in all the remaining countries)

For the final (Week 52) analysis additionally the following subgroups will be presented:

- Adrenal Insufficiency status measured when a participant reaches 5mg of daily OCS dose: Normal, Partial AI, Complete AI.
- Countries: for the list of countries see Section 4.1.1.1

Subgroup analyses are performed on the FAS. If any of the subgroups have fewer than 10 participants in a level, then this subgroup level is not included in any model. If that leaves only one subgroup level, the analysis is not performed for that categorical variable.

4.2.1.8 Interim Analysis of Primary Endpoint

The derivation of the final daily maintenance OCS dose as described in Section 4.2.1.2 cannot be applied due to the reason mentioned in Section 4.2. Alternatively, for each post-baseline visit the latest daily maintenance OCS dose at the time of the visit is used as described in Section 4.2.7.2.

The number and proportion of participants who discontinued OCS or reduced OCS dose to ≤ 5 mg/day is summarised over time on the FAS.

4.2.2 Secondary Endpoint - Annual asthma exacerbation rate (AAER) over Week 28 and Week 52

4.2.2.1 Definition

To support the secondary objective assessing the ability of tezepelumab 210 mg SC to prevent asthma exacerbations in adult participants with OCS-dependent asthma while OCS dose reduction, the AAER over 28 weeks and over 52 weeks are calculated.

An asthma exacerbation is defined in Section 1.2.

4.2.2.2 Derivations

The start and end date of the asthma exacerbation is collected in the EXACA eCRF form. The asthma exacerbation duration is derived as *Exacerbation end date - Exacerbation start date +1*.

The AAER (in years) over the study treatment period of interest (Week 28 or Week 52) is calculated as the total number of asthma exacerbations over the Week 28 or Week 52 divided by the total time at risk calculated for Week 28 or Week 52, respectively, on the FAS. Derivation of time at risk over 28 or 52 weeks is detailed in two steps.

Derivation of time at risk is presented in Table 5.

Table 5. Time at risk derivation over 28 or 52 weeks

	If a participant attended visit of interest (Visit 9/Week 28 or Visit 15/EOT Week 52)	if visit of interest (Visit 9/Week 28 or Visit 15/EOT Week 52) is not available for a participant
Time at risk over 28 weeks (years)	[earliest (date of Visit 9, date of another biologic initiation) – date of first IP dose + 1 – sum of (asthma exacerbations + 7days[b])] / 365.25	[earliest {date of first IP dose + 196 days + 5 days; date of another biologic initiation, latest(date of last available visit including IPD visit, date of death, date of last exacerbation assessment status from the EXACD eCRF form)} – date of first IP dose + 1 – sum of (asthma exacerbations + 7days[b])] / 365.25
Time at risk over 52 weeks (years)	[earliest (date of Visit 15[a], date of last exacerbation assessment status from EXACD eCRF form, date of another biologic initiation – date of first IP dose + 1 – sum of (asthma exacerbations + 7 days[b])] / 365.25	[{earliest (date of first IP dose + 365 days + 5 days, date of last exacerbation assessment status from the EXACD eCRF form, date of another biologic initiation, date of death) – date of first IP dose} + 1 – sum of (asthma exacerbations + 7 days[b])] / 365.25

[a] The date of Visit 15 is used irrespective of how late this may have occurred in relation to the protocol schedule.
[b] 7 days should be added to each asthma exacerbation duration as no asthma exacerbation can occur during that time.

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, 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 ER 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 IP.

The exacerbations that occur after a participant has discontinued IP 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 on IP or not.

Any exacerbations that start 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.

4.2.2.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.2.4 Primary Analysis of Secondary Endpoint

Number and percentages of participants with at least one exacerbation as well as with specific number of exacerbations (0, 1, etc.) is presented. The number of exacerbations per participant as well as total days of exacerbations and total days of exacerbations per participant is be presented.

The total number of exacerbations, total time at risk (years) and AAER estimated as defined in Section 4.2.2.2 are presented over 28 and over 52 weeks. In addition, 95% confidence interval is calculated based on exact Poisson confidence interval.

The summaries are presented be based on the FAS.

4.2.2.5 Additional Analyses of Secondary Endpoint

No additional analysis.

4.2.2.6 Subgroup Analyses of Secondary Endpoint

The analysis described in Section 4.2.2.4 is repeated in subgroups described in Section 4.2.1.7.

4.2.2.7 Interim Analysis of Secondary Endpoint

No presentation for interim analysis.

4.2.3 Secondary Endpoint - Rate of asthma exacerbation associated with hospitalisation over 28 weeks and over 28 weeks and 52 weeks

4.2.3.1 Definition

Two rates of asthma exacerbation are assessed:

- Annualized rate of asthma exacerbation associated with hospitalisation or emergency room (ER) visit over 28 weeks and over 52 weeks.
- Annualized rate of asthma exacerbation associated with hospitalisation over 28 weeks and over 52 weeks.

Exacerbations due to hospitalisations or ER visits and exacerbations associated with the hospitalisations are a subset of all asthma exacerbations.

4.2.3.2 Derivations

Both endpoints are similarly derived to AAER including all asthma exacerbations as described in Section 4.2.2.2 but based on the selected asthma exacerbations, i.e., associated with hospitalisation or emergency room (ER) visit or associated with hospitalisation only.

4.2.3.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.3.4 Primary Analysis of Secondary Endpoint

The same analysis as described in Section 4.2.2.4 is presented but including exacerbations associated with hospitalisation or emergency room (ER) or with hospitalisation only. The analyses are performed based on the FAS.

4.2.3.5 Additional Analyses of Secondary Endpoint

No additional analysis.

4.2.3.6 Subgroup Analyses of Secondary Endpoint

The analysis described in Section 4.2.3.4 is repeated in subgroups described in Section 4.2.1.7.

4.2.3.7 Interim Analysis of Secondary Endpoint

No presentation for interim analysis.

4.2.4 Secondary Endpoint - Proportion of participants who did not experience an exacerbation at Week 28 and Week 52.

4.2.4.1 Definition

There are three proportions to assess this secondary endpoint:

- Proportion of participants who did not experience an exacerbation,
- Proportion of participants who did not experience an exacerbation associated with hospitalization or ER visit,
- Proportion of participants who did not experience an exacerbation associated with hospitalization.
- Each of those proportion of participants (i.e., who did not experience an exacerbation; an exacerbation associated with hospitalization or ER visit; an exacerbation associated with hospitalization only) are calculated over 28 weeks and over the 52-week period.

4.2.4.2 Derivations

For considering a participant without any experience of exacerbation, the planned treatment period defined in Section 3.3.1.1 has to be considered. A participant is considered to have completed the planned treatment period, if the planned treatment period is greater than

- than 191 (Day 196 minus 5) for the analysis at Week 28
- 359 days (Day 364 minus 5, to account for visit windowing) for the analysis at Week 52

Participants who had no asthma exacerbations during the planned treatment period and who completed the period of interest (up to Week 28 or Week 52) without initiating another biologic are defined as exacerbation free/successful outcome [a].

Participants who did not complete the planned treatment period or initiate another biologic during the planned treatment period are defined as not having a successful outcome for this endpoint [b] [c].

Participants who completed the planned treatment period without initiating another biologic and had an asthma exacerbation are defined as not having a successful outcome for this endpoint [d].

	No asthma exacerbation	Asthma exacerbation
Completed planned treatment period without initiating another biologic	[a] Exacerbation free/successful outcome	[d] No successful outcome
Did not complete treatment period or initiate another biologic during the planned treatment period	[b] No successful outcome	[c] No successful outcome

The proportion is calculated as the number of participants with a successful outcome at Week 28/Week 52 divided by total number of participants in the FAS population.

The proportion of participants free from exacerbations that required hospitalisation or ER visits (or hospitalization only) during the planned treatment period is calculated similarly. A participant who only had an exacerbation which did not lead to hospitalisation or ER visit (or hospitalisation only) is considered a successful outcome for this endpoint.

4.2.4.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.4.4 Primary Analysis of Secondary Endpoint

The number and proportions of participants who did not experience an exacerbation, an exacerbation associated with hospitalisation or ER visit and an exacerbation associated with hospitalisation are summarised using the same approach described for the primary endpoint (Section 4.2.1.4) on the FAS.

4.2.4.5 Additional Analyses of Secondary Endpoint

No additional analysis.

4.2.4.6 Subgroup Analyses of Secondary Endpoint

The analysis described in Section 4.2.4.4 is repeated in subgroups described in Section 4.2.1.7.

4.2.4.7 Interim Analysis of Secondary Endpoint

No presentation for interim analysis.

4.2.5 Secondary Endpoint - Proportion of participants with ≥ 50% reduction from baseline in daily maintenance OCS dose at Week 28 and Week 52

4.2.5.1 Definition

The proportion of participants with ≥ 50% reduction from baseline in daily maintenance OCS dose is calculated at Week 28 and at Week 52.

4.2.5.2 Derivations

The percent change from baseline in final daily maintenance OCS dose is defined as presented in Section 3.3. The baseline and final daily maintenance OCS dose derivation are defined in Sections 3.3.1.2 and 4.2.1.2. The proportion is calculated as the number of participants with the percent change from baseline ≥ 50% divided by total number of participants in the FAS.

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 participants with ≥ 50% reduction from baseline in daily maintenance OCS dose are summarised using the same approach described for the primary endpoint (Section 4.2.1.4) on the FAS.

4.2.5.5 Additional Analyses of Secondary Endpoint

No additional analysis.

4.2.5.6 Subgroup Analyses of Secondary Endpoint

The analysis described in Section 4.2.5.4 is repeated in subgroups described in Section 4.2.1.7.

4.2.5.7 Interim Analysis of Secondary Endpoint

The derivation of baseline, post-baseline and change from baseline in daily maintenance OCS dose is described in Section 4.2.7.2.

The number and proportion of participants with ≥ 50% reduction from baseline in daily maintenance OCS dose is summarised over time on the FAS.

4.2.6 Secondary Endpoint - Categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 and Week 52.

4.2.6.1 Definition

The proportion of participants for each reduction categories from baseline in the daily maintenance OCS dose are calculated at Week 28 and Week 52.

4.2.6.2 Derivations

The percentage reduction from baseline in daily maintenance OCS dose at Week 28 and at Week 52 whilst maintaining asthma control is calculated as described in Section 3.3 and categorised as follows:

- Category 1: ≥ 90% to ≤100% reduction
- Category 2: ≥75% to <90% reduction
- Category 3: ≥50% to <75% reduction
- Category 4: >0% to <50% reduction
- Category 5: no change or any increase.

The baseline and final daily maintenance OCS dose derivation are defined in Sections 3.3.1.1 and 4.2.1.2.

4.2.6.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.6.4 Primary Analysis of Secondary Endpoint

The number and proportions of participants in each categorised percent reduction from baseline in the final daily maintenance OCS dose at Week 28 and Week 52 are summarised using the same approach described for the primary endpoint (Section 4.2.1.4) on the FAS.

4.2.6.5 Additional Analyses of Secondary Endpoint

No additional analysis.

4.2.6.6 Subgroup Analyses of Secondary Endpoint

The analysis described in Section 4.2.6.4 is repeated in subgroups described in Section 4.2.1.7.

4.2.6.7 Interim Analysis of Secondary Endpoint

No presentation for interim analysis.

4.2.7 Secondary Endpoint - Absolute and percent change from baseline in daily maintenance OCS dose at Week 28 and Week 52.

4.2.7.1 Definition

The absolute and percent changes from baseline in the daily maintenance OCS dose are calculated at Week 28 and Week 52.

4.2.7.2 Derivations

The daily OCS dose at Visit X is the latest OCS dose during this visit. Note the visit windows for daily OCS dose per visits are based on actual visit dates as described in Section 3.3.2.

The absolute and percent change from baseline in daily OCS dose at a post-baseline visit is calculated as defined in Section 3.3 on the FAS. The baseline daily maintenance OCS dose derivation is defined in Section 3.3.1.2. The derivation of daily OCS dose at a post-baseline visit is defined in Section 4.2.1.2.

The data selected for the analysis are described in Section 4.2.1.2.

4.2.7.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.7.4 Primary Analysis of Secondary Endpoint

The absolute values as well as absolute and percent change from baseline in daily maintenance OCS dose is summarised using descriptive statistics over time on the FAS. All data available at primary DBL is presented, which includes data beyond Week 28 (see Section 3.1).

The percent change from baseline in daily maintenance OCS dose is analysed using a model for repeated measures. The percent change from baseline at each post-baseline visit up to and including Week 28 (Week 52 for the Week 52 analysis) is the dependent variable in the model. The visit is included as a categorical covariate and the OCS dose at baseline and logarithm of baseline blood eosinophils count are included as continuous covariates in the model. The analysis is performed on participants in the FAS who have an OCS baseline and at least one non-missing post baseline value. Participant is included in the model using the REPEATED statement (no RANDOM statement is specified). The variance-covariance

matrix is assumed to be unstructured. If the model does not converge, then compound symmetry matrix is used. The Kenward-Roger approximation to estimating the degrees of freedom is used for tests of fixed effects derived from the model.

The adjusted mean changes from baseline together with its 95% CI are estimated from this model, tabulated and presented graphically over time.

The relation between the percent change from baseline in daily maintenance OCS dose at Week 28 (Week 52) and each continuous baseline biomarker variable separately (EOS, FeNO, and total IgE) is estimated following nonparametric approach such as a locally estimated scatterplot smoothing (LOESS) plot or a generalized additive model (GAM). The model-based percent change from baseline at Week 28 (Week 52) is presented together with 95% confidence band on the graphs against the baseline biomarker variable.

4.2.7.5 Additional Analyses of Secondary Endpoint

No additional analysis.

4.2.7.6 Subgroup Analyses of Secondary Endpoint

The analysis described in Section 4.2.7.4 is repeated in subgroups described in Section 4.2.1.7.

4.2.7.7 Interim Analysis of Secondary Endpoint

The derivation of baseline, post-baseline and change from baseline in daily maintenance OCS dose is described in Section 4.2.7.2.

The absolute values as well as absolute and percentage change from baseline in daily maintenance OCS dose are presented over time on the FAS.

4.2.8 Secondary Endpoint - Change from baseline in post-BD FEV_1 at Week 28 and Week 52.

4.2.8.1 Definition

The change from baseline in post-bronchodilator FEV_1 is calculated at Week 28 and Week 52.

4.2.8.2 Derivations

The absolute change from baseline in post-BD FEV1 at a post-baseline visit is calculated as described in Section 3.3 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.

4.2.8.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.8.4 Primary Analysis of Secondary Endpoint

The absolute values and absolute changes from baseline in post-BD FEV1 are summarised using descriptive statistics over time. All data available at primary DBL is presented, which includes data beyond Week 28 (see Section 3.1).

The same statistical analysis as described in Section 4.2.7.4 is applied for the absolute change from baseline in post-BD FEV1. The baseline of post-BD FEV1 is used as covariate instead of the baseline OCS dose.

The analyses are performed based on the FAS.

4.2.8.5 Additional Analyses of Secondary Endpoint

No additional analysis

4.2.8.6 Subgroup Analyses of Secondary Endpoint

The analysis described in Section 4.2.8.4 is repeated in subgroups described in Section 4.2.1.7.

4.2.8.7 Interim Analysis of Secondary Endpoint

The absolute values and absolute changes from baseline in post-BD FEV1, derived as described in Section 4.2.8.2, are presented over time on the FAS.

4.2.9 Secondary Endpoint - Change from baseline in Asthma Control Questionnaire 6 (ACQ-6) at Week 28 and Week 52

4.2.9.1 Definition

The ACQ-6 questionnaire includes the following questions:

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 of the ACQ-6 are measured on a 7-point scale scored from 0 (totally controlled) to 6 (severely uncontrolled).

This endpoint is the change from baseline in Asthma Control Questionnaire 6 (ACQ-6) at Week 28 and Week 52.

4.2.9.2 Derivations

The ACQ-6 score is computed as the unweighted mean of the responses to the 6 questions presented above. Higher scores indicate poorer outcomes. If response to any of the questions is missing, the ACQ-6 is automatically set to missing (directly managed at the data entry level).

The absolute change from baseline in Asthma Control Questionnaire 6 (ACQ-6) score at a post-baseline visit is calculated for participants on the FAS as described in Section 3.3. Baseline value is derived as presented in Section 3.3.1.2. Strategies of handling intercurrent events are presented in Section 4.2.

4.2.9.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.9.4 Primary Analysis of Secondary Endpoint

The absolute values and absolute changes from baseline in ACQ-6 score are summarised using descriptive statistics over time. All data available at primary DBL is presented, which includes data beyond Week 28 (see Section 3.1).

The same statistical analysis as described in Section 4.2.7.4 is applied for the absolute change from baseline in ACQ-6 score except that the visit covariate is replaced by weekly timepoints and the baseline of ACQ-6 is used as covariate instead of the baseline OCS.

The analyses are performed based on the FAS.

4.2.9.5 Additional Analyses of Secondary Endpoint

No additional analysis.

4.2.9.6 Subgroup Analyses of Secondary Endpoint

The analysis described in Section 4.2.9.4 is repeated in subgroups described in Section 4.2.1.7.

4.2.9.7 Interim Analysis of Secondary Endpoint

The absolute values and changes from baseline in ACQ-6 score, derived as described in Section 4.2.9.2, are presented over time on the FAS.

4.2.10 Secondary Endpoint - Change from baseline in standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ[s]+12) total score at Week 28 and Week 52

4.2.10.1 Definition

In the AQLQ(S) +12 the participants are asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment).

The AQLQ(S) +12 change in total score from baseline at Week 28 and Week 52 is calculated for all participants.

4.2.10.2 Derivations

The total score is calculated as the mean response to all questions. The 4 individual domain scores (4 domains assessing: symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. Higher scores indicate better outcomes. The following are the question numbers on the AQLQ(S) +12 questionnaire relating to each domain:

Table 6 AQLQ(S) +12 domains

Domain	AQLQ(S) +12 question number
Symptoms	6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitations	1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function	7, 13, 15, 21, 27
Environmental Stimuli	9, 17, 23, 26

If response to any of the questions is missing, the AQLQ(S) +12 total score is automatically set to missing. If response to a question within a domain is missing, the score for that domain is automatically set to missing. It is directly managed at the data entry level.

The absolute change from baseline in AQLQ(S)+12 total score and in each domain at a post-baseline visit are calculated as described in Section 3.3 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 Secondary Endpoint

The absolute values and absolute changes from baseline in total AQLQ(S)+12 score and in each domain are summarised using descriptive statistics over time. All data available at primary DBL is presented, which includes data beyond Week 28 (see Section 3.1).

The same statistical analysis as described in Section 4.2.7.4 is applied for the absolute change from baseline in total AQLQ(S)+12 score. The baseline of total AQLQ(S)+12 score is used as covariate instead of the baseline OCS.

The analyses are performed based on the FAS.

4.2.10.5 Additional Analyses of Secondary Endpoint

No additional analysis.

4.2.10.6 Subgroup Analyses of Secondary Endpoint

The analysis described in Section 4.2.10.4 is repeated in subgroups described in Section 4.2.1.7 for the absolute change from baseline in AQLQ(s)+12 total score.

4.2.10.7 Interim Analysis of Secondary Endpoint

No presentation for interim analysis.

4.2.11 Secondary Endpoint - Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 28 and Week 52

4.2.11.1 Definition

The SGRQ is a 50-item PRO instrument developed to measure the health status of participants with airway obstruction diseases. 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 domain 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.

The St. George's Respiratory Questionnaire (SGRQ) total score change from baseline at Week 28 and Week 52 is calculated for all participants. The change from baseline is also calculated for each of the 3 domains.

4.2.11.2 Derivations

Absolute change from baseline in SGRQ total score and for each domain at a post-baseline visit are calculated as described in Section 3.3 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.

If response to any of the questions is missing, the SGRQ total score is automatically set to missing. If response to a question within a domain is missing, the score for that domain is automatically set to missing. It is directly managed at the data entry level.

4.2.11.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.11.4 Primary Analysis of Secondary Endpoint

The absolute values and absolute changes from baseline in SGRQ total score and in each domain are summarised using descriptive statistics over time. All data available at primary DBL is presented, which includes data beyond Week 28 (see Section 3.1).

The same statistical analysis as described in Section 4.2.7.4 is applied for the absolute change from baseline in SGRQ total score. The baseline of SGRQ total score is used as covariate instead of the baseline OCS. In addition, the model for primary DBL at Week 28 does not include visit as a covariate as well as participant is not included in the REPEATED statement (i.e., ANCOVA model).

The analyses are performed based on the FAS.

4.2.11.5 Additional Analyses of Secondary Endpoint

No additional analysis.

4.2.11.6 Subgroup Analyses of Secondary Endpoint

The analysis described in Section 4.2.11.4 is repeated in subgroups described in Section 4.2.1.7 for the absolute change from baseline in SGRQ total score.

4.2.11.7 Interim Analysis of Secondary Endpoint

No presentation for interim analysis.

4.2.12 Exploratory Endpoint - Changes from baseline in biomarker levels at Week 28 or Week 52

4.2.12.1 Definition

The changes from baseline in biomarker (EOS, FeNO, IgE) levels at Week 28 or Week 52 is calculated for all participants in the FAS.

4.2.12.2 Derivations

The absolute changes from baseline in biomarker (EOS, FeNO, IgE) levels at a post-baseline visit are calculated as described in Section 3.3 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.

4.2.12.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.12.4 Primary Analysis of Exploratory Endpoint

The absolute values and changes from baseline in biomarker levels are summarised using descriptive statistics over time on the FAS. All data available at primary DBL is presented, which includes data beyond Week 28 (see Section 3.1).

4.2.12.5 Additional Analyses of Exploratory Endpoint

No additional analysis.

4.2.12.6 Subgroup Analyses of Exploratory Endpoint

No subgroup analysis.

4.2.12.7 Interim Analysis of Exploratory Endpoint

The absolute values and changes from baseline in biomarker levels, derived as described in Section 4.2.12.2, are summarised over time on the FAS.

4.2.13 Exploratory Endpoint - Time to 50% and 100% reduction of OCS dose over Week 28 and Week 52

4.2.13.1 Definition

The time to reach 50% and 100% OCS dose reduction from baseline over Week 28 and Week 52 is presented for all participants in the FAS.

4.2.13.2 Derivations

The derivation of baseline OCS maintenance dose is defined in Section 3.3.1.2. The OCS dose in mg/day is derived using therapy reasons given in Section 3.3. The percent change from baseline in OCS dose/day is calculated as presented in Section 3.3 on the FAS. Strategies of handling intercurrent events are presented in Section 4.2.

The time (in days) from first IP dose to achieve 50% reduction of OCS dose for the 1st time are calculated as follows:

Time to 50% OCS reduction (days) = (Date of 50% OCS reduction from baseline achieved for the 1st time – date of IP dose) + 1.

If there is no sufficient OCS dose reduction (i.e. percentage OCS dose reduction < 50%) during 28 (or 52) weeks or prior to initiation of another biologic, participants are censored at earliest[date of Visit 9/Week 28 if available or date of first IP dose +196 days if visit not done (or date of the Visit 15/Week 52 if available or date of first IP dose + 364 days if visit not available), date of initiation of another biologic].

The Time to 100% OCS reduction (days) is calculated using the same approach described for the 50% OCS reduction on the FAS.

4.2.13.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.13.4 Primary Analysis of Exploratory Endpoint

Number and percentages of participants who achieved OCS reduction thresholds (for both 50% and 100%) are summarised at Week 28 and Week 52.

Time to OCS reductions is analysed using the Kaplan-Meier estimates. A Kaplan-Meier plot is presented as well as summary tables including adjusted median time to event along with 95% confidence interval calculated using the Kaplan-Meier estimate respectively for 50% and 100% OCS reduction thresholds until Week 28 and Week 52.

The analyses are performed based on FAS.

4.2.13.5 Additional Analyses of Exploratory Endpoint

No additional analysis.

4.2.13.6 Subgroup Analyses of Exploratory Endpoint

No subgroup analysis.

4.2.13.7 Interim Analysis of Exploratory Endpoint

The derivation of baseline, post-baseline and change from baseline in daily maintenance OCS dose is described in Section 4.2.7.2. The time (in days) to achieve 50% or 100% reduction of OCS dose for the 1st time is derived as presented in Section 4.2.13.2.

The results are presented as described in Section 4.2.13.4.

4.2.14 Exploratory Endpoint - Proportion of participants with normal, partial, complete AI at Week 28 and Week 52

4.2.14.1 Definition

For all participants, the hypothalamic-pituitary-adrenal (HPA) axis integrity is evaluated after 4 weeks on 5 mg/day and prior to tapering down the OCS dose. If the result of HPA

test is in indeterminate range, the additional ACTH/HPA test is required. More details is given in CSP Section 8.2.1.

The proportion of participants with normal, indeterminate and complete AI based on HPA test, the proportion of participants with normal, partial and complete AI based on ACTH test as well as the proportion of participants with normal, partial and complete AI based on the repeated HPA test are summarised at Week 28 or Week 52.

4.2.14.2 Derivations

The three proportions of participants with normal, indeterminate and complete AI based on morning cortisol test are calculated as the total number of participants with the normal, indeterminate and complete AI respectively divided by total number of participants on the FAS.

The three proportions of participants with normal, partial and complete AI based on ACTH test are calculated as the total number of participants with the normal, partial and complete AI respectively divided by total number of participants requiring additional ACTH testing.

The three proportions of participants with normal, partial and complete AI based on repeated morning cortisol test are calculated as the total number of participants with the normal, partial and complete AI respectively divided by total number of participants requiring repeated morning cortisol testing for whom ACTH test is not available.

Strategies of handling intercurrent events are presented in Section 4.2.

4.2.14.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.14.4 Primary Analysis of Exploratory Endpoint

The number and proportions of participants with normal, indeterminate and complete AI based on morning cortisol test are summarised over time on the FAS. In addition, if the morning cortisol test is in indeterminate range, the number and proportions of participants with normal, partial and complete AI based on ACTH test as well as repeated morning cortisol test are presented.

4.2.14.5 Additional Analyses of Exploratory Endpoint

No additional analysis.

4.2.14.6 Subgroup Analyses of Exploratory Endpoint

No subgroup analysis.

4.2.14.7 Interim Analysis of Exploratory Endpoint

No presentation for interim analysis.

4.2.15 Exploratory Endpoint - Proportion of ACQ-6 responders at Week 28 and Week 52

4.2.15.1 Definition

The proportion of responders are summarised at each timepoint until and including Week 28 or Week 52. Individual changes of at least 0.5 are considered to be clinically meaningful and a decrease from baseline of at least 0.5 is the responder definition for ACQ-6.

4.2.15.2 Derivations

ACQ-6 responder (Yes=1/No=0) is calculated at each timepoint as follows:

- Responder: Absolute individual change from baseline in ACQ-6 score ≤ -0.5
- Non-responder: Absolute individual change from baseline in ACQ-6 score > -0.5

The proportion of responders (non-responders) is calculated as the number of participants who reached the responder (non-responder) ACQ-6 threshold at each timepoint divided by total number of participants in the FAS.

Strategies of handling intercurrent events are presented in Section 4.2.

4.2.15.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.15.4 Primary Analysis of Exploratory Endpoint

The number and proportions of ACQ-6 responders, non-responders and missing data are summarised over time on the FAS. Additionally, the percentage of ACQ-6 responders is displayed graphically over time.

4.2.15.5 Additional Analyses of Exploratory Endpoint

No additional analysis.

4.2.15.6 Subgroup Analyses of Exploratory Endpoint

No subgroup analysis.

4.2.15.7 Interim Analysis of Exploratory Endpoint

The derivation of ACQ-6 responder is presented in Section 4.2.15.2.

The number and proportions of ACQ-6 responders, non-responders and missing data are presented over time on the FAS.

4.2.16 Exploratory Endpoint - Proportion of AQLQ(s)+12 responders at Week 28 and Week 52

4.2.16.1 Definition

The AQLQ(s)+12 responders are summarised at Week 28 or Week 52. The responder definition for AQLQ(s)+12 is 0.5-point improvement from baseline.

4.2.16.2 Derivations

AQLQ(s)+12 responder (Yes=1/No=0) is calculated on the FAS at each timepoint as follows:

- Responder: Absolute individual change from baseline in AQLQ(s)+12 total score ≥ 0.5
- Non-responder: Absolute individual change from baseline in AQLQ(s)+12 total score < 0.5

The proportion of responders (non-responders) is calculated as the number of participants who reached the responder (non-responder) AQLQ(s)+12 threshold at each timepoint divided by total number of participants in the FAS.

Strategies of handling intercurrent events are presented in Section 4.2.

4.2.16.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.16.4 Primary Analysis of Exploratory Endpoint

The number and proportions of AQLQ(s)+12 responders, non-responders and missing data are summarised over time on the FAS.

4.2.16.5 Additional Analyses of Exploratory Endpoint

No additional analysis.

4.2.16.6 Subgroup Analyses of Exploratory Endpoint

No subgroup analysis.

4.2.16.7 Interim Analysis of Exploratory Endpoint

No presentation for interim analysis.

4.2.17 Exploratory Endpoint - Proportion of SGRQ responders at Week 28 and Week 52

4.2.17.1 Definition

The responders on SGRQ are summarised at Week 28 or Week 52. A change score of 4 units is associated with a minimum clinically important difference (MCID). The responder definition for SGRQ is a decrease of at least 4 score from baseline.

4.2.17.2 Derivations

SGRQ responder (Yes=1/No=0) is calculated on the FAS at each timepoint as follows:

- Responder: Absolute individual change from baseline in total SGRQ score ≤ -4
- Non-responder: Absolute individual change from baseline in total SGRQ score > -4

The proportion of responders (non-responders) is calculated as the number of participants who reached the responder (non-responder) SGRQ threshold at each timepoint divided by total number of participants in the FAS.

Strategies of handling intercurrent events are presented in Section 4.2.

4.2.17.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.17.4 Primary Analysis of Exploratory Endpoint

The number and proportions of SGRQ responders, non-responders and missing data are summarised over time on the FAS.

4.2.17.5 Additional Analyses of Exploratory Endpoint

No additional analysis.

4.2.17.6 Subgroup Analyses of Exploratory Endpoint

No subgroup analysis.

4.2.17.7 Interim Analysis of Exploratory Endpoint

No presentation for interim analysis.

4.2.18 Exploratory Endpoint - Change from baseline in AIRQ and proportion of responders at Week 52

4.2.18.1 Definition

AIRQ contains 10 binary questions about respiratory symptoms, activity limitation, sleep, rescue medication use, social activities, exercise, difficulty controlling asthma, and exacerbations. The AIRQ total score change from baseline to Week 52 and the AIRQ

responder rate are calculated at Week 52. The responder definition for AIRQ is a decrease from baseline of at least 2 scores.

4.2.18.2 Derivations

Each positive answer ("Yes") is converted to 1. The AIRQ score for a participant is the sum of all positive answers. A higher score indicates worse asthma control status. If response to any of the questions is missing, the AIRQ is automatically set to missing (directly managed at the data entry level).

The absolute change from baseline in AIRQ score at Week 52 is calculated as described in Section 3.3 on the FAS. Baseline value is derived as presented in Section 3.3.1.2.

Responder (Yes=1/No=0) is calculated at each timepoint as follows:

- Responder: Absolute individual change from baseline in AIRQ score ≤ -2
- Non-responder: Absolute individual change from baseline in AIRQ score > -2

The proportion of responders (non-responders) is calculated as the number of participants who reached the responder (non-responder) AIRQ threshold at Week 52 divided by total number of participants in the FAS.

Strategies of handling intercurrent events are presented in Section 4.2.

4.2.18.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.18.4 Primary Analysis of Exploratory Endpoint

The absolute value and absolute change from baseline in AIRQ score at Week 52 are summarised using descriptive statistics. The number and proportions of AIRQ responders, non-responders and missing data at Week 52 are also presented.

The analyses are performed based on the FAS.

4.2.18.5 Additional Analyses of Exploratory Endpoint

No additional analysis.

4.2.18.6 Subgroup Analyses of Exploratory Endpoint

No subgroup analysis.

4.2.18.7 Interim Analysis of Exploratory Endpoint

No presentation for interim analysis.

4.2.19 Exploratory Endpoint - Change from baseline in Sino-nasal Outcome Test (SNOT-22) and responder rate at Week 28 and Week 52

4.2.19.1 Definition

The SNOT-22 is a 22-item health-related outcomes assessment for sinonasal conditions and restricted to participants with history of chronic sinusitis at baseline. Each item is scored as 0 (no problem) to 5 (problem as bad as it can be).

The absolute changes from baseline in SNOT-22 are calculated at Week 28 and Week 52. The responder definition for SNOT-22 is a decrease of at least 8.9 scores from baseline (Hopkins et al, 2009).

4.2.19.2 Derivations

The SNOT-22 score is the sum of the 22 items and it ranges from 0 to 110. Higher scores indicate poorer outcomes. If one or more of the individual items is missing, the total SNOT-22 score is automatically set to missing (directly managed at the data entry level).

The absolute change from baseline in SNOT-22 score at a post-baseline visit is calculated as described in Section 3.3 on the FAS. Baseline value is derived as presented in Section 3.3.1.2.

Responder (Yes=1/No=0) is calculated on the FAS at each timepoint as follows:

- Responder: Absolute individual change from baseline in SNOT-22 score $\leq$ -8.9
- Non-responder: Absolute individual change from baseline in SNOT-22 score > -8.9

The proportion of responders (non-responders) is calculated as the number of participants who reached the responder (non-responder) SNOT-22 threshold at each timepoint divided by total number of participants in the FAS.

Strategies of handling intercurrent events are presented in Section 4.2.

4.2.19.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.19.4 Primary Analysis of Exploratory Endpoint

The absolute values and absolute changes from baseline in SNOT-22 score are summarised using descriptive statistics over time. The number and proportions of SNOT-22 responders, non-responders and missing data are also presented over time. All data available at primary DBL is presented, which includes data beyond Week 28 (see Section 3.1).

The analyses are performed based on the FAS.

4.2.19.5 Additional Analyses of Exploratory Endpoint

No additional analysis.

4.2.19.6 Subgroup Analyses of Exploratory Endpoint

No subgroup analysis.

4.2.19.7 Interim Analysis of Exploratory Endpoint

No presentation for interim analysis.

4.2.20 Exploratory Endpoint - Changes from baseline in Participant Perception of OCS (PPOCS) score at Week 28 and Week 52

4.2.20.1 Definition

The PPOCS questionnaire includes two following questions:

1. *How bothered are you by the side effects of your current oral steroid dose?* The question is asked only at baseline.
2. *How have the side effects of your current oral steroid dose changed since starting this study?* The question is asked at Week 28 and Week 52.

4.2.20.2 Derivations

Response for the first question at baseline is derived as presented in Section 3.3.1.2. The second question already includes the change from baseline. There is no need for additional derivation. Strategies of handling intercurrent events are presented in Section 4.2.

There is no data manipulation required for responses. They are treated as categorical variables.

4.2.20.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.20.4 Primary Analysis of Exploratory Endpoint

The number and percentages of participants selected specific response for each question are presented at baseline, Week 28 and Week 52.

4.2.20.5 Additional Analyses of Exploratory Endpoint

No additional analysis.

4.2.20.6 Subgroup Analyses of Exploratory Endpoint

No subgroup analysis.

4.2.20.7 Interim Analysis of Exploratory Endpoint

No presentation for interim analysis.

4.2.21 Exploratory Endpoint - Mean daily exposure of systemic corticosteroids (mg/day) taken for asthma reasons over 28 and 52 weeks

4.2.21.1 Definition

The mean daily exposure of systemic corticosteroids (SCS; mg/day) taken for asthma reasons is calculated over 28 and 52 weeks. The endpoint allows for an assessment of the overall load of SCS for asthma reasons during the planned treatment period, in addition to maintenance OCS.

4.2.21.2 Derivations

The mean daily exposure of systemic corticosteroids (SCS) taken for asthma reasons is calculated for all participants in the FAS using all 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 the CSP Appendix D.

The endpoint is calculated according the following formula:

The mean daily exposure of SCS (mg/day) over 28 (or 52) weeks = Cumulative SCS dose over 28 (or 52) weeks (mg) / minimum(total number of days in the 28-week (or 52) planned treatment period, total number of days from the first IP dose until initiation of another biologic).

where:
Cumulative SCS dose over 28 (or 52) weeks (mg) = sum of daily SCS dose over 28 (52) weeks of the planned treatment period or earlier if another biologic is initiated.

Strategies of handling intercurrent events are presented in Section 4.2.

4.2.21.3 Handling of Dropouts and Missing Data

No data imputation.

4.2.21.4 Primary Analysis of Exploratory Endpoint

The mean daily exposure of systemic corticosteroids at Week 28 and Week 52 is summarised using descriptive statistics (n, mean, standard deviation, median, minimum and maximum).

In addition, the cumulative SCS dose (mg) is summarised using descriptive statistics (n, mean, standard deviation, median, minimum and maximum) over time on the FAS. The average of the cumulative SCS dose (mg, +/- 1 Standard Error) over the planned treatment

period is presented graphically over time (days). All data available at primary DBL is presented, which includes data beyond Week 28 (see Section 3.1).

4.2.21.5 Additional Analyses of Exploratory Endpoint

No additional analysis.

4.2.21.6 Subgroup Analyses of Exploratory Endpoint

No subgroup analysis.

4.2.21.7 Interim Analysis of Exploratory Endpoint

The derivation of cumulative SCS dose (mg) is presented in Section 4.2.21.2.

The cumulative SCS dose (mg) is summarised over time on the FAS.

4.3 Pharmacodynamic Endpoint

No pharmacodynamic endpoints evaluated in the study.

4.4 Pharmacokinetics Endpoint

No pharmacokinetic endpoints evaluated in the study.

4.5 Immunogenicity

No immunogenicity endpoints evaluated in the study.

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 IP (DAEs), adverse events of special interest (AESIs), and laboratory test results. All safety variables are summarised using the FAS.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Extent of exposure to IP is defined as the number of days between the date of first dose of IP and the date of last dose of IP inclusive plus the number of days allowance for the dosing interval specified in Section 3.3.1.1, that is:

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

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

4.6.1.2 Presentation

Exposure to IP is summarised using descriptive statistics (mean, standard deviation, median, minimum and maximum) based on the FAS. In addition, the number of dosing occasions are also summarised on the FAS.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

Adverse events, categorised as Serious Adverse Events (SAEs), SAEs with outcome of death, Adverse Events leading to discontinuation of IP (DAEs), Adverse Events of special interest (AESIs) defined in the CSP Section 8.3.6, experienced by the participants were collected throughout the entire study and coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse event data is categorized according to their onset date into the following study periods:

- AEs in the pre-treatment period are defined as those with onset day before day of first dose of study treatment.
- AEs in the on-treatment period are defined as those with onset day between the day of first dose of study treatment and earliest (date of last dose of IP + 33 days, date of death, date of study withdrawal).
- AEs in the post-treatment period are defined as those with onset after the end of on-treatment period defined above until the study completion or withdrawal date.
- AEs in the on-study period are defined as those with onset between day of first dose of study treatment and the study completion or withdrawal date.

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.

AEs that have missing causality (after data querying) is assumed to be related to study drug.

Liver adverse events and evaluation of Hy's Law are submitted as a SAE and is described accordingly. Hy's Law cases are listed with their related laboratories parameters. Details regarding Potential Hy's Law and Hy's Law are given in the CSP Appendix F2.

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' extend 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 summarised, or one or more occurrences of that event.

4.6.2.2 Presentation

Adverse events are summarised separately for the on-treatment and on-study periods unless specified otherwise. Adverse events occurring during the screening period, or occurring post-treatment is listed, but not summarised separately.

An overall summary table is produced showing the number and percentage of participants with at least 1 adverse event in any of the following categories: Serious Adverse Events (SAEs), SAEs with outcome of death, AEs leading to discontinuation of investigational product (DAEs). The number of events in the different AE categories is also presented. The summaries are accounted for multiple occurrences of the same event in a participant.

The number and percentage of participants with an SAE, SAEs with outcome of death and AESI (each category separately) are presented by System Organ Class (SOC) and Preferred Term (PT) assigned to the event using the MedDRA dictionary for on-treatment and on-study period. For each PT, the number and percentage of participants reporting at least one occurrence is presented (i.e., multiple occurrences of an AE for a participant are only counted once). SOCs and PTs are sorted by international order (the Internationally Agreed Order of SOCs was developed for consistency irrespective of language or alphabet. The SOC order was based upon the relative importance of each SOC in AE reports). In addition, the exposure-adjusted SAE and AESI (each category separately) summaries are presented by SOC and PT. The number and percentage of participants with SAEs are presented sorted by decreasing frequency on PT level for on-treatment and on-study period. The DAE are presented by SOC and PT for on-treatment period only.

On-treatment SAEs, DAEs, and AESIs (each category separately) are also summarised by SOC, PT and causality/relatedness (as determined by the investigator). Information about maximum intensity, of AEs is listed. If a participant reports multiple occurrences within each PT, the maximum intensity is taken as the highest recorded (the order being mild, moderate, and severe) respectively.

Key subject information of SAEs, DAEs and AESIs for on-study is presented.

The handling of partial/missing dates for AEs is detailed in Appendix A. Duration of AEs is not calculated using imputed dates and instead set to missing.

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

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.

Presentation of Adverse events for interim analysis

The number and percentage of participants with at least 1 adverse event in any of the following categories: Serious Adverse Events (SAEs), SAEs with outcome of death, AEs leading to discontinuation of investigational product (DAEs) is presented for on-study period. The number of events in the different AE categories is also presented.

The number and percentage of participants with SAEs are presented by System Organ Class (SOC) and Preferred Term (PT) as well as sorted by decreasing frequency on PT level for on-study period.

Key subject information of AESIs is presented.

All summaries for interim analysis are presented on the FAS.

4.6.3 Clinical Laboratory, Blood sample

4.6.3.1 Definitions and Derivations

Blood samples for determination of clinical chemistry, haematology and serology (Hepatitis B and C) parameters are taken at Visit 1 (Week -4 to Week 0) and assessed in a central laboratory. Central laboratory normal reference ranges are used for the identification of individual clinically important abnormalities, classified as low (below range), normal (within range or on the limits) or high (above range).

4.6.3.2 Presentations

Laboratory data are summarised by descriptive statistics (mean, standard deviation, median, lower and upper quartile, minimum and maximum). The clinically important abnormalities per categories presented in Section 4.6.3.1 are listed.

Laboratory data are presented on-study period only.

All data are summarised including data from unscheduled visits and repeated measurements according to the visit window presented in Section 3.3.2.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

Urine HCG is performed only for female participants at the times detailed in the CSP.

4.6.4.2 Presentations

No results will be listed/summarised, the analysis of positive results remains outside the scope of this Statistical Analysis Plan.

4.6.5 Other Laboratory, Evaluations

4.6.5.1 Definitions and Derivations

Other laboratory tests are applicable to female participants only and conducted at Visit 1 (Week -4 to 0). Serum β-HCG and Follicle-stimulating hormone for female participants lower than 50 years who have been amenorrhoeic for ≥ 12 months.

4.6.5.2 Presentations

No results will be listed/summarised, the analysis of positive results remains outside the scope of this Statistical Analysis Plan.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

The weight and height are measured according to the schedule described in CSP Section 1.3. BMI is calculated according to the formula presented in Section 4.1.5. Absolute change from baseline is calculated as described in Section 3.3 for weight and BMI.

4.6.6.2 Presentations

Observed values of weight, height and BMI are summarised at each timepoint they are measured by means of descriptive statistics (mean, standard deviation, median, lower and upper quartile, minimum and maximum). The on-study period is used to summarise the data. In addition, for weigh and BMI absolute change from baseline is also presented over time.

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

Not collected.

4.6.7.2 Presentations

Not applicable

4.6.8 Other Safety Assessments

Not applicable

5 INTERIM ANALYSIS

An interim analysis may be performed if approximately 50 participants complete V4 before a data cut-off date planned on mid-April 2023. All data available for participants who completed Visit 4 prior to the data cut-off date will be included. The results are not used to change any element of the study design and the study continues regardless of the results of interim analysis.

6 REFERENCES

Hopkins et al, 2009
Hopkins C, Gillett S, Slack R, Lund V.J & Browne, J.P. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin. Otolaryngol. 2009, 34, 447–454.

7 APPENDIX

Appendix A Partial dates for adverse events and prior/concomitant medications

Dates missing the day, or both the day and month of the year adhere to the following conventions to classify treatment-emergent AEs (TEAEs) and to classify prior/concomitant medications:

- The missing start day is set to:
    - First day of the month of occurrence, if the start YYYY-MM is after the YYYY-MM of first study treatment
    - The day of the first study treatment, if the start YYYY-MM is the same as YYYY-MM of the first study treatment
    - The date of informed consent, if the onset YYYY-MM is before the YYYY-MM of the first study treatment.
- The missing end day is set to:
    - The last day of the month of the occurrence, if the end YYYY-MM is after the YYYY-MM of the first study treatment.
    - Death date if the participant died in the same month.
    - The day of last study treatment if the YYYY-MM of occurrence is the same as the last study treatment.
- If the start date is missing both the day and month, the start date is set to:
    - January 1 of the year of occurrence.
    - The date of the first study treatment, if the start year is the same as the year of the first study treatment
- If the end date is missing both the day and month, the date is set to:
    - December 31 of the year of occurrence.
    - Date of death if the participant died in the same year.
    - Last study treatment date if the year of occurrence is the same as the last study treatment date.

- If the start date is null, the date is set to:
    - The date of first study treatment.
    - January 1 of the same year as the end date, if the end date suggests that the start date could be prior to the date of first study treatment.
- If the end date is null and not recorded as ongoing, the date is set to:
    - The date of the first study treatment, if the start date is prior to the date of first study treatment.
    - The date of last visit, if the start date is on or after the date of first study treatment.
- If the end date is null and recorded as ongoing, the end date is not imputed.

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