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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

TEZSPIRE

Tezepelumab

Procedure no: EMA/PAM/0000340081

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start date	27 April 2026	27 April 2026
☐	CHMP Rapporteur AR	1 June 20262	29 May 2026
☐	CHMP comments	15 June 2026	n/a
☐	Updated CHMP Rapporteur AR	18 June 2026	n/a
☐	CHMP outcome	25 June 2026	25 June 2026
☐	Submission date	30 June 2026	30 June 2026
☐	Re-Start date	1 July 2026	1 July 2026
☐	CHMP Rapporteur AR	8 July 2026	6 July 2026
☐	CHMP comments	13 July 2026	n/a
☐	Updated CHMP Rapporteur AR	16 July 2026	n/a
☒	CHMP outcome	23 July 2026	23 July 2026

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1. Introduction

On 31 March 2026, the MAH submitted a completed paediatric study for TEZSPIRE, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This study is not included in the PIP and is submitted as a stand-alone Article 46 submission in accordance with the requirements of the Paediatric Regulation. A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Tezepelumab is a fully human immunoglobulin 2λ monoclonal antibody directed against Thymic stromal lymphopoietin (TSLP), which is an epithelial cytokine that is produced in response to proinflammatory stimuli and drives inflammatory responses, primarily through its activity on dendritic, Type 2 innate lymphoid cells and mast cells. Blocking TSLP can inhibit multiple biologic pathways involved in asthma.

The TSLP molecule is a heterotetramer consisting of 2 heavy chains of IgG2 subclass and 2 light chains of the λ subclass, which are covalently linked through disulfide bonds. Tezepelumab binds with human TSLP and prevents its interaction with TSLP receptor complex.

Tezepelumab received a marketing authorisation as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment valid throughout the EU on 19 September 2022.

The MAH stated that Study D5180C00032, titled 'a multicentre, single-arm, open-label, post-authorisation, Phase 4 effectiveness and safety study of tezepelumab in adult and adolescent participants with severe asthma including several under-studied populations in the United States' (PASSAGE) is a stand-alone study.

The MAH has stated that there are no amendments to be introduced to Product Information as a result of the study completion, as the results do not influence the benefit-risk profile for tezepelumab.

2.2. Information on the pharmaceutical formulation used in the study

The study treatment used in this study was Tezspire 210 mg solution administered via subcutaneous injection Q4W. Study treatment was provided either in 5 mL vials or accessorized pre-filled syringes [APFS]. Individual batch numbers and further information are included in the CSR.

2.3. Clinical aspects

Introduction

The MAH submitted a final study report and clinical expert overview for:

- Study D5180C00032, 'A multicentre, single-arm, open-label, post-authorisation, Phase 4 effectiveness and safety study of tezepelumab in adult and adolescent participants with severe asthma including several under-studied populations in the United States' (PASSAGE)

Clinical study

Study D5180C00032 (PASSAGE)

Description

Study D5180C00032 (PASSAGE) was a multicentre, single-arm, open-label, post-authorisation, Phase 4 effectiveness and safety study of tezepelumab in adult and adolescent participants with severe asthma including several under-studied populations in the US.

The purpose of PASSAGE was to assess the effectiveness of tezepelumab in the US among a broader and more representative population than Phase 3 RCTs. The study population consisted of adults and adolescent participants with asthma requiring medium-dose to high-dose ICS with additional controller(s) for at least 12 months prior to Visit 1, and with documented history of at least 2 asthma exacerbations in the prior year.

The study population included a broad population of participants across traditional asthma phenotypes of high and low blood eosinophils and allergic status, as well as four eligible but under-studied populations:

- individuals who identify as Black/African American
- adolescents (12-17 years)
- those with a comorbid diagnosis of mild to moderate COPD consistent with GOLD guidelines
- those with significant smoking history (≥ 10 pack-years of smoking).

These four under-studied populations have an estimated prevalence of 10 - 16% of US severe asthma population and were under-represented or excluded from Phase 3 RCTs.

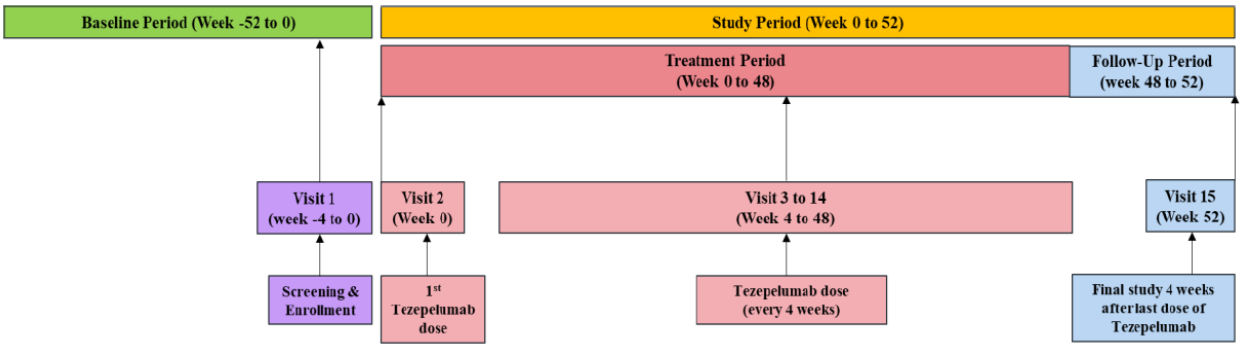
The study compromised the following study periods and visits:

- **Baseline Period (Weeks -52 to 0)**: The baseline period was defined as the 12 months prior to the index date (Week 0). A 12-month baseline period of relevant historical data (through medical record review) was required prior to index date for all participants to allow for a standardized period of history to describe selected participant demographics, comorbidities, asthma disease burden, and previous medication use.
    - **Screening Window (Weeks -4 to 0)**: Eligibility criteria were checked at Visit 1.
    - **Enrolment date**: Enrolment date was allowed to be on the same day of screening (Visit 1) or after, but before any mandatory study-specific procedures.
        - Participants were asked to complete PRO questionnaires, lung function assessment, and clinical/laboratory tests at Visit 1 or before dosing at Visit 2.
- **Treatment Period (Week 0 to 48)**: The treatment period with tezepelumab dose was from Visit 2 (Week 0) until Visit 14 (Week 48).
- **Follow-up period (Weeks 48 to 52)**: The follow-up period included the post-dosing follow-up period (Weeks 48 to 52) and EOT assessment at Visit 15 (Week 52).
    - Participants visited the Investigator's site every 4 weeks for tezepelumab administration and routine care.
    - During Visit 8 (Week 24) and Visit 15 (Week 52), participants were asked to complete PRO questionnaires, lung function assessment, and/or clinical and laboratory tests.

- All SAEs, DAEs, and AESIs were recorded from the index date, throughout the tezepelumab treatment period (Weeks 0 to 48) and post-dosing follow-up period (Weeks 48 to 52).
- Participants were observed from their index date until the earliest of the following events: (1) Death, (2) Withdrawal of consent, (3) Lost to follow-up, or (4) End of the 12-month post-baseline period

Figure 1 shows the design of the study and the sequence of treatment periods.

Figure 1. Schematic of Study Design



Methods

Study participants

Participants with documented physician-diagnosed asthma for at least 12 months prior to Visit 1, male or female, 12 years of age or older, receiving treatment with medium-to-high dose ICS as per GINA 2021 guidelines (daily dose of fluticasone propionate >250-500 µg to >500 µg or equivalent) along with additional asthma maintenance controller medication(s), and a documented history of at least 2 asthma exacerbations during the previous year, were eligible for inclusion in this study.

Treatments

Tezepelumab 210 mg was administered subcutaneously every 4 weeks (up to 13 doses from Weeks 0 to 48). The 210 mg dosage is the same dosage that has been approved for adults and adolescents in the US and EU. Single use APFS were utilized to deliver the study intervention under study.

Objectives and endpoints

Table 1. Objectives and Endpoints (Ref. table 1, CSR)

Objectives	Estimand Description/Endpoints
Primary Objective	
To describe asthma exacerbations [a] in the 12-month periods before (Baseline Period) and after initiation of tezepelumab (study period)	**Endpoints** • AAER over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period) **Supportive endpoints** • Proportion of participants with asthma exacerbations over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period) • Proportion of participants who completed the 52-week Study Period following tezepelumab initiation with any reduction, at least 50% reduction, and 100% reduction in total number of asthma exacerbations • Cumulative asthma exacerbation days over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period)
	Population: Adults and adolescents with asthma requiring medium- to high-dose ICS, requiring additional controller(s), and those with at least 2 asthma exacerbations in the prior year who received at least one dose of tezepelumab **Intercurrent events:** • Treatment discontinuation: All available data will be included for participants in the full analysis set (treatment policy strategy) • Initiation of other non-biologic medication for asthma: All available data will be included for participants in the full analysis set (treatment policy strategy). • Initiation of other biologics for asthma: All data after the start of another biologic for asthma will be set to missing in the analyses (hypothetical strategy).

Objectives	Estimand Description/Endpoints
	Summary measure: Annual asthma exacerbation rate ratio and corresponding 95% CI for 52 weeks after initiation of tezepelumab vs 52 weeks before initiation of tezepelumab
Secondary Objectives	
To describe the time to first exacerbation after initiation of tezepelumab	• Time to first asthma exacerbation
To describe asthma exacerbations resulting in hospitalizations, ED/UC visits in the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period)	• Rate of asthma exacerbations associated with hospitalizations over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period) • Rate of asthma exacerbations associated with ED/UC visits over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period) • Rate of asthma exacerbations associated with hospitalizations or ED/UC over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period) • Proportion of participants with asthma exacerbations [a] associated with hospitalizations or ED/UC visits over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period) • Cumulative asthma exacerbations associated with hospitalizations or ED/UC visits over 52 weeks before (Baseline Period) and after initiation of tezepelumab (study period)
To describe lung function at baseline and months 6 and 12 after initiation of tezepelumab	• Pre-BD FEV1 • Change from baseline in pre-BD FEV1 • Proportion of pre-BD FEV1 responders (defined as participants who achieve either at least 5% or 100 mL improvement from baseline)
To describe ACQ-6, AIRQ, and SGRQ at baseline and months 6 and 12 after initiation of tezepelumab	• ACQ-6 score • AIRQ score • SGRQ score • Change from baseline in ACQ-6 score • Change from baseline in AIRQ score • Change from baseline in SGRQ score • Proportion of ACQ-6 responders (defined as participants who achieve ≥ 1 MCID [b]) • Proportion of AIRQ responders (defined as participants who achieve ≥ 1 MCID [b]) • Proportion of SGRQ responders (defined as participants who achieve ≥ 1 MCID [b])

Objectives	Estimand Description/Endpoints
To describe SCS use in the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period)	• Proportion of participants who require any SCS use • Cumulative annualized SCS dose • Proportion of participants who require longer-term (> 30 consecutive days) SCS use
To describe asthma-related HRU in the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period)	• Number and type of asthma-related HRU • Duration of asthma-related hospitalizations
To describe asthma exacerbations and asthma-related HRU in the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period) in the following subgroups of participants defined at baseline: • BEC ≥ 300 cells/microliter • BEC < 300 cells/microliter • With a clinically-relevant allergy to a perennial aeroallergen [c] • Without a clinically-relevant allergy to a perennial aeroallergen [c] • Participants who identify as Black/African American • Adolescents (12-17 years) • Comorbid diagnosis of mild to moderate COPD [d] • Significant smoking history (≥ 10 pack-years of smoking)	• AAER over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period) • Proportion of participants with asthma exacerbations [a] over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period) • Proportion of participants who completed the 52-week Study Period following tezepelumab initiation with any reduction, at least 50% reduction, and 100% reduction of total number of asthma exacerbations • Cumulative asthma exacerbation days over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period) • Rate of asthma exacerbations associated with hospitalizations over 52 weeks before (baseline period) and after initiation of tezepelumab (Study Period) • Rate of asthma exacerbations associated with ED/UC visits over 52 weeks before (baseline period) and after initiation of tezepelumab (Study Period) • Rate of asthma exacerbations associated with hospitalizations or ED/UC visits over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period) • Number and type of asthma-related HRU • Duration of asthma-related hospitalizations
Safety Objectives	
To describe the safety and tolerability of tezepelumab	• Occurrence of SAEs, DAEs, and AESIs
Exploratory Objectives	
To describe adherence/persistence, duration of therapy, discontinuation, and reasons for discontinuation after initiation of tezepelumab	• Duration of tezepelumab treatment • Frequency of discontinuation/interruption of tezepelumab treatment • Time to discontinuation of tezepelumab treatment and reasons • Time interval between tezepelumab administrations [g]

Objectives	Estimand Description/Endpoints
	• Number of administered tezepelumab injections [g] • Number of switches to other biologic treatments and biologics class
To describe lung function at months 6 and 12 after initiation of tezepelumab	• Change from baseline in post-BD FEV_1 value • Change from baseline in FEV_1 reversibility after 52 weeks
To describe asthma exacerbations and asthma-related HRU (sample permitting for exploratory subgroup of participants [a, f]) during the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period)	• AAER before (Baseline Period) and after initiation of tezepelumab (Study Period) • Proportion of participants with asthma exacerbations over 52 weeks • Cumulative asthma exacerbation days over 52 weeks before (Baseline Period) and after initiation of tezepelumab (Study Period) • Proportion of participants who completed the 52-week Study Period following tezepelumab initiation with any reduction, at least 50% reduction, and 100% reduction of total number of asthma exacerbations • Number and type of asthma-related HRU • Annualized rate of ED/UC visits associated with asthma exacerbations • Annualized rate of hospitalizations associated with asthma exacerbations • Duration of asthma-related hospitalizations
To describe TSQM-9 and physician CGI-C in months 6 and 12 after initiation of tezepelumab	• TSQM-9 score • CGI-C score
To describe FPC [e] at 6 and 12 months after initiation of tezepelumab	• Change from baseline in FPC composite score
To describe the participants' assessment of their COPD symptoms in participants with ongoing diagnosis of COPD (prior to tezepelumab dosing at Visit 2 at 6 and 12 months after initiation of tezepelumab)	• Patient's PGI-C score for COPD
To describe TNSS at baseline and months 6 and 12 after initiation of tezepelumab	• TNSS score • Change from baseline for TNSS score among participants with baseline symptoms • Proportion of TNSS responders among participants with baseline symptoms (defined as participants who achieve $\geq$ 1 MCID [b]) [g]
To describe participant-reported causes of asthma symptoms or asthma attacks as reported within an Asthma Trigger Survey at baseline and month 12, and asthma exacerbations and asthma-related HRU (sample permitting) during the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period) as a function of	• Number and proportion of participants with reported trigger/number of triggers • Change from baseline for reported triggers/number of triggers • Asthma exacerbations and HRU ie, as a function of reported triggers/number of triggers

Objectives	Estimand Description/Endpoints
participant-reported trigger categories/number of reported triggers	
To describe tezepelumab-treated participants meeting the study-specific definition of clinical remission	• Number and proportion of participants who achieve asthma clinical remission
To describe SNOT-22 (only among participants with ongoing diagnosis of chronic rhinosinusitis with or without nasal polyps at baseline regardless of whether symptoms are present on the day of Visit 1 or 2) at months 6 and 12 after initiation of tezepelumab	• SNOT-22 total score • Change from baseline in SNOT-22 total score • Proportion of SNOT-22 responders (defined as participants who achieve ≥1 MCID [b])
Qualitative interview data to explore participant experiences after initiation of tezepelumab across the subgroups of selected participants	• Testimonials of treatment response

[a] Asthma exacerbation was defined by worsening of asthma symptoms that led to temporary bolus/burst of systemic corticosteroids for at least 3 consecutive days, or an ED/UC visit due to asthma that required SCS (per above), and/or inpatient hospitalizations (≥ 24 hours) due to asthma. The Investigator had to justify the decision for defining an event of worsening asthma as an exacerbation.

[b] Minimum clinically important difference was defined in the SAP (Appendix 16.1.9).

[c] Defined as a clinical history of asthma symptoms driven by exposure to a perennial aeroallergen and sensitization to the corresponding aeroallergen(s) based on a positive result to serum allergen-specific IgE testing by FEIA at baseline.

[d] Consistent with GOLD 2021 guidelines.

[e] FPC is a composite endpoint that can be calculated using two SGRQ items: "Over the past 3 months, I have coughed…" and "Over the past 3 months, I have brought up phlegm (sputum)…".

[f] Exploratory subgroup of participants was defined in the SAP (Appendix 16.1.9).

[g] Refer to Section 9.9.2.1

Sample size

The sample size of 400 participants was based on practical considerations and the ability to obtain at least 50 participants in the major subgroups of interest. A total of 331 participants were screened; 286 received the study intervention and were included in the final analysis. Of these, 251 (87.8%) participants completed treatment, and 255 (89.2%) completed the study; 31 (10.8%) participants discontinued before study completion.

The study was conducted at 32 study sites in the United States of America. The first patient was screened in this study on 11 May 2022, and the last patient completed the last study visit on 01 October 2025. The analyses presented in the CSR are based on a clinical data lock date of 19 November 2025.

Randomisation and blinding (masking)

This was a single-arm, open-label study; thus, no randomization or blinding was required.

Statistical Methods

There was no predefined study hypothesis to test in this study, as such, no multiplicity control strategy was applied. This study was descriptive in nature; hence, all analyses followed an estimation-based approach.

Efficacy

The primary objective of this study was to describe and compare the rates of asthma exacerbations in the 12-month baseline period and the 12-month post-baseline period of treatment with tezepelumab.

This was achieved by performing an analysis of the incidence of exacerbations 12 months after the index date (Week 0) compared to the baseline period (the 12 months prior to the index date).

The annual exacerbation rate was defined as the sum of exacerbations occurring among all participants during the specified period divided by the total person-time at risk in days and multiplied by 365.25. Time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation cannot occur, was subtracted from the time at risk derivation over the Baseline and Study Periods.

Any asthma exacerbation that occurred within 7 days of the last dose of SCS, a temporary increase in stable OCS background dose, date of ED/UC visits or date of hospital discharge for a prior exacerbation was counted as the same exacerbation event.

For the primary analysis, the exacerbation rate was analysed using a GEE model for repeated measures, using a log link function. The annual asthma exacerbation rate ratio and corresponding 95% CI were presented.

The supportive endpoints of the primary endpoint were presented descriptively.

Safety

Safety and tolerability of tezepelumab were assessed from SAEs, SAEs with outcome of death, DAEs, AESIs, and laboratory tests. Laboratory data were summarized by summary statistics. All safety analyses, including per-participant listings, were summarized using the FAS.

Results

Participant flow

A total of 286 participants received the study intervention. During the study period (Week 0 to Week 52), no participants had temporary interruptions of tezepelumab treatment. Of the 286 participants, 251 (87.8%) participants completed treatment and 255 (89.2%) completed the study.

A total of 35 (12.2%) participants permanently discontinued treatment, with the most common reasons being participant decision (18, 6.3% participants), AEs (8, 2.8% participants), and loss to follow-up (4, 1.4% participants). Thirty-one (10.8%) participants withdrew from the study, primarily due to withdrawal by participant (16, 5.6% participants) and loss to follow-up (6, 2.1% participants). There were 2 deaths (0.7%) reported during the study.

Seventy-six (26.6%) participants had allergic asthma with BEC ≥300 cells/μL, 45 (15.7%) participants had non-allergic asthma with BEC ≥300 cells/μL, 89 (31.1%) participants had allergic asthma with BEC <300 cells/μL, and 74 (25.9%) participants had non-allergic asthma with BEC <300 cells/μL.

The study intentionally enrolled underrepresented populations:

- 63 (22.0%) participants were Black/African American
- 19 (6.6%) participants were adolescents
- 57 (19.9%) participants had comorbid diagnosis of mild to moderate COPD
- 83 (29.0%) participants were smokers (≥10 pack-years).

Table 2. Disposition (All Participants Analysis Set) (Ref. table 6, CSR)

	Total n (%)
Overall	
Participants screened [a]	331
Screen failures	38
Withdrawal by participant	3
Other	4
Participants started treatment	**286 (100)**
Participants completed treatment	251 (87.8)
Participants discontinued treatment	35 (12.2)
Adverse event	8 (2.8)
Consent withdrawal	2 (0.7)
Investigator decision	1 (0.3)
Participant decision	18 (6.3)
Participant lost to follow-up	4 (1.4)
Pregnancy	2 (0.7)
Participants who discontinued treatment but completed the study	6 (2.1)
Participants completed study	255 (89.2)
Participants withdrawn from study	31 (10.8)
Death	2 (0.7)
Development of study-specific withdrawal criteria	2 (0.7)
Lost to follow-up	6 (2.1)
Other	5 (1.7)
Withdrawal by participant	16 (5.6)

[a] Screened participants were those who signed informed consent (enrolled participants).

Only the final screen fail reasons were counted if multiple screenings occurred for the same participant. The same subject may have met multiple screen failure reasons. Percentages were based on the number of participants who started treatment. Positive (ie, allergic): Any perennial FEIA positive. Negative (ie, Non-allergic): All available perennial FEIA negative. Unknown: No FEIA test results were available.

n = Number of participants per category.

Protocol deviations

Overall, 68 (23.8%) participants had at least one important protocol deviation (IPD) during the study. The most common category of IPDs was 'procedure/tests' (44 [15.4%] participants). The other most frequent IPDs were 'inclusion/exclusion criteria' (15 [5.2%] participants), 'AE/SAE' (9 [3.1%] participants, i.e., "SAE not reported on time"), and 'informed consent' (7 [2.4%]).

Table 3. Important protocol deviations (Full Analysis Set) (Ref. table 7, CSR)

	Teze 210 mg Q4W N = 286 n (%)
Participants with at least one IPD	68 (23.8)
AE SAE	9 (3.1)
Inc/Excl Criteria	15 (5.2)
Informed Consent	7 (2.4)
Procedures/Tests	44 (15.4)
Participants with at least one IPD related to global/country situation	0
Participants with at least one IPD, excluding global/country related IPDs	68 (23.8)
AE/SAE	9 (3.1)
Inc/Excl Criteria	15 (5.2)
Informed Consent	7 (2.4)
Procedures/Tests	44 (15.4)

N = Number of participants; n = Number of participants per category.

Number analysed

All Participants Analysis Set (all participants screened) included 331 participants. The Full Analysis Set (FAS) included all enrolled participants who received at least one dose of tezepelumab (286 participants), irrespective of their protocol adherence and continued participation in the study. All safety and efficacy analyses were performed using the FAS. For consistency, demographics and baseline characteristics were presented using the FAS.

Demographic and baseline data

The overall demographics and key baseline characteristics of the study participants are summarized for the Full analysis set in Table 4 below. Overall, the mean age of participants was 52.9 years (range: 12 to 80 years), and 100 (35.0%) participants were male, and 186 (65.0%) participants were female. The majority of participants were White (204 [71.3%]), Not Hispanic or Latino (259 [90.6%]), and aged ≥18 to < 65 years (190 [66.4%]).

Table 4. Baseline demographics (Full analysis set)

	Statistics or category	Teze 210 mg Q4W
Overall		**N = 286**
Age (years)	n	286
	Mean	52.9
	SD	16.2
	Median	57.0
	Min	12
	Max	80
Age group (years), n (%)	≥ 12 - < 18	19 (6.6)
	≥ 18 - < 65	190 (66.4)
	≥ 65	77 (26.9)
Sex, n (%)	Female	186 (65.0)
	Male	100 (35.0)
Race, n (%)	White	204 (71.3)
	Black or African American	63 (22.0)
	Asian	8 (2.8)
	Native Hawaiian or Other Pacific Islander	1 (0.3)
	American Indian or Alaska Native	4 (1.4)
	Multiple	0
	Not reported	2 (0.7)
	Other	4 (1.4)
Ethnicity, n (%)	Hispanic or Latino	27 (9.4)
	Not Hispanic or Latino	259 (90.6)

N = Number of participants; n = Number of participants in analysis for a continuous variable and number of participants category for a categorical variable.

Baseline Asthma and COPD Characteristics

Overall, 207 (72.4%) participants had severe GINA asthma diagnosis, and 71 (24.8%) participants had moderate asthma diagnosis. The majority of asthma triggers were allergen triggers (240 [83.9%] participants). The mean (SD) asthma duration was 26.95 (20.35) years and mean (SD) age at onset of asthma was 26.5 (21.8) years.

Overall, 22 (7.7%) participants had comorbid diagnosis of mild COPD, and 35 (12.2%) participants had comorbid diagnosis of moderate COPD. The mean (SD) COPD duration was 7.20 (7.39) years.

Overall, 285 (99.7%) participants had at least one asthma exacerbation in the baseline period. The mean (SD) number of asthma exacerbations per participant in the baseline period was 2.5 (1.3). About 36 (12.6%) participants had at least one asthma exacerbation resulting in hospitalisation in the baseline period. The mean (SD) number of asthma exacerbations resulting in hospitalisation per participant in the baseline period was 0.2 (0.5).

The mean (SD) pre-BD FEV1 was 2.160 (0.735) L; 172 (60.1%) participants had pre-BD FEV1 (% Predicted) ≤80%. The mean (SD) daily SCS dose was 32.7207 (11.1342) mg. The mean (SD) cumulative annualised SCS was 3671.7044 (24494.7408) mg.

Rapporteur's comments:

The planned sample size for this study was approximately 400 participants, with the goal of including at least 50 individuals in each of the key subgroups of interest. In total, 331 participants were screened of whom 286 received study intervention and were included in the final analysis set. Recruitment targets were exceeded in three of the four predefined subgroups; participants who were Black/African American (n=63), participants with a comorbid diagnosis of mild to moderate COPD (n=57), and smokers (≥10 pack-years) (n=83). However, enrolment in the adolescent subgroup (≥12 - <18 years of age) was limited, with only 19 participants included.

A total of 286 participants were enrolled and received the study intervention, with high completion rates (87.8% for treatment, 89.2% for study). Overall, the study population was representative of the target population with severe, uncontrolled asthma, including by asthma phenotypes (allergic and non-allergic asthma across varying blood eosinophil levels) and under-represented populations. It is worth noting that although the study was multicentre, it was restricted to sites in the US, which may limit the generalisability of the findings to populations in other geographic regions and healthcare settings.

The study was an open-label, single-arm design. The lack of a comparator treatment arm (placebo or active) makes it difficult to definitively attribute observed outcomes to tezepelumab rather than natural disease variation, background therapy, or placebo effects. The open label nature can result in reporting and assessment bias, particularly for symptom control or QoL endpoints.

Nonetheless, the study does provide post-marketing data on effectiveness, strengthens safety knowledge, and address uncertainties regarding underrepresented populations identified at the time of approval. These data need to be interpreted alongside existing randomised trial data.

The primary objective of this study was to describe asthma exacerbations in the 12-month periods before (Baseline Period) and after initiation of tezepelumab (Study Period). Secondary and exploratory endpoints aimed to further characterize asthma exacerbation rates in this population.

The safety objective of this study was to describe the safety and tolerability of tezepelumab and was based on evaluation of the following endpoints: occurrence of SAEs, AEs that lead to tezepelumab treatment discontinuation, and AESIs.

Overall, 68 (23.8%) participants had at least one important protocol deviation (IPD) during the study. The majority of these involved procedures/tests not completed at the correct timepoint during the study. None of the identified IPDs were considered to have a major impact on the study results and conclusions.

Efficacy results

Primary Endpoint: Annualised Asthma Exacerbation Rate (AAER)

During the 12-month Baseline Period, 285 of 286 participants (99.7%) experienced at least one asthma exacerbation, with a total of 713 exacerbations occurring over 247.90 participant years at risk, resulting in an annual asthma exacerbation rate of 2.8762 per year. The mean (SD) number of exacerbations per participant was 2.5 (1.3), with a median of 2.0 (range: 0 to 12). At baseline, 261 participants (91.3%) had at least 2 exacerbations, meeting the inclusion criterion of ≥2 documented asthma exacerbations.

During the 12-month Study Period after initiation of tezepelumab, 120 of 286 participants (42.0%) experienced at least one exacerbation, with a total of 226 exacerbations over 260.93 participant-years

at risk, corresponding to an annual asthma exacerbation rate of 0.8661 per year. The mean (SD) number of exacerbations per participant decreased to 0.8 (1.3), with a median of 0.0 (range: 0 to 8).

Statistical analysis using a GEE model for repeated measures revealed a reduction in AAER during the Study Period compared to the Baseline Period. The rate ratio (study vs. baseline) was 0.30 (95% CI: 0.25, 0.37), indicating a reduction in the AAER following tezepelumab initiation.

Table 5. Annualised asthma exacerbation rate in the Baseline and Study Period (Full Analysis Set)

							Comparison with baseline period		
Period	n	Number of events	Total time at risk	Crude rate	Adjusted rate	95% CI	Rate ratio	95% CI	p-value
Overall									
Study Period, Visit 15 (12 months)	286	226	260.93	0.8661	0.8665	(0.71, 1.05)	0.30	(0.25, 0.37)	< 0.001
N = 286									
Baseline Period (12 months)	286	713	247.90	2.8762	2.8783	(2.69, 3.08)			
N = 286									
Baseline BEC < 300 cells/microliter and with all perennial FEIA negative									
Study Period, Visit 15 (12 months)	74	83	64.40	1.2888	1.2936	(0.92, 1.81)	0.46	(0.34, 0.62)	< 0.001
N = 74									
Baseline Period (12 months)	74	184	64.07	2.8721	2.8269	(2.51, 3.18)			
N = 74									
Baseline BEC < 300 cells/microliter and with any perennial FEIA positive									
Study Period, Visit 15 (12 months)	89	59	80.13	0.7363	0.7345	(0.51, 1.06)	0.26	(0.18, 0.38)	< 0.001
N = 89									
Baseline Period (12 months)	89	217	77.29	2.8075	2.8020	(2.55, 3.08)			
N = 89									
Baseline BEC ≥ 300 cells/microliter and with all perennial FEIA negative									
Study Period, Visit 15 (12 months)	45	30	42.55	0.7050	0.7032	(0.45, 1.10)	0.25	(0.15, 0.40)	< 0.001
N = 45									
Baseline Period (12 months)	45	113	39.44	2.8654	2.8677	(2.41, 3.41)			
N = 45									
Baseline BEC ≥ 300 cells/microliter and with any perennial FEIA positive									
Study Period, Visit 15 (12 months)	76	51	71.90	0.7093	0.7175	(0.49, 1.06)	0.23	(0.15, 0.36)	< 0.001
N = 76									
Baseline Period (12 months)	76	195	65.26	2.9881	3.0649	(2.56, 3.67)			
N = 76									
Black or African American									
Study Period, Visit 15 (12 months)	63	51	56.28	0.9062	0.9007	(0.61, 1.34)	0.27	(0.18, 0.41)	< 0.001
N = 63									
Baseline Period (12 months)	63	178	54.44	3.2697	3.2865	(2.81, 3.85)			
N = 63									
Adolescents									
Study Period, Visit 15 (12 months)	19	12	17.76	0.6756	0.6684	(0.34, 1.30)	0.29	(0.14, 0.59)	< 0.001
N = 19									
Baseline Period (12 months)	19	40	17.06	2.3451	2.3218	(1.97, 2.74)			
N = 19									
Phase II: Comorbid diagnosis of mild to moderate COPD									
Study Period, Visit 15 (12 months)	57	49	51.78	0.9462	0.9377	(0.60, 1.46)	0.35	(0.22, 0.54)	< 0.001
N = 57									
Baseline Period (12 months)	57	136	49.76	2.7332	2.7046	(2.42, 3.03)			
N = 57									
Baseline smoking status: ≥ 10 pack-years of smoking									
Study Period, Visit 15 (12 months)	83	77	73.96	1.0411	1.0363	(0.74, 1.46)	0.36	(0.26, 0.50)	< 0.001
N = 83									
Baseline Period (12 months)	83	210	72.39	2.9009	2.8811	(2.63, 3.16)			
N = 83									

Model: GEE model for repeated measures was applied, using log link function. The response variable was the number of exacerbations in each period following negative binomial distribution. The covariates were period (Baseline Period, Study Period) and age (continuous). The logarithm of the time at risk was used as an offset variable. The unstructured covariance matrix structure was used. Baseline Period (12 months): The Baseline Period was defined as the 12-months prior to the index date (Week -52 to Week 0). Study Period, Visit 15 (Week 0 to Week 52): The Study Period consisted of the treatment period (Week 0 to Week 48) and the follow-up period (Week 48 to 52). A rate ratio less than 1 indicated that in the Study Period it was shown [1-rate ratio)] × 100% reduction in AAER as compared to the Baseline Period. NC was added because there were less than 10 participants in that subgroup or when the subgroup had less than 3 participants who experienced exacerbation in each study population.

N = Number of participants; n = Number of participants in analysis.

All subgroups demonstrated reductions in AAER from the Baseline Period to the Study Period, with rate ratios ranging from 0.23 to 0.46. Reductions in AAER were observed across all prespecified asthma phenotypes, including participants with baseline BEC ≥300 cells/μL and any perennial aeroallergen sensitization (rate ratio 0.23, 95% CI: 0.15, 0.36) and those with baseline BEC <300 cells/μL and no perennial aeroallergen sensitization (rate ratio 0.46, 95% CI: 0.34, 0.62).

Consistent reductions were also observed in underrepresented populations, including Black/African American participants (rate ratio 0.27, 95% CI: 0.18, 0.41), adolescents aged 12 to 17 years (rate ratio 0.29, 95% CI: 0.14, 0.59), participants with ≥10 pack-year smoking history (rate ratio 0.36, 95% CI: 0.26, 0.50), and those with comorbid mild to moderate COPD (rate ratio 0.35, 95% CI: 0.22, 0.54).

Supportive Endpoint: Proportion of Participants with Exacerbation Reductions-Supplementary Analysis

At 12 months (Visit 15):

- The proportion of participants achieving at least a 50% reduction in exacerbations was 209 (73.1%).
- The number of participants with a 100% reduction in exacerbations was 148 (51.7%).
- The proportion of subgroup participants achieving at least 50% reduction ranged from 59.5% (nonallergic with BEC <300 cells/μL) to 80.0% (non-allergic with BEC ≥300 cells/μL), while 100% reduction rates ranged from 43.2% (non-allergic with BEC <300 cells/μL) to 57.8% (non-allergic with BEC ≥300 cells/μL).
- Total cumulative days in exacerbation decreased from 8,855 days (mean (SD): 31.0 (26.4) days per participant) during the Baseline Period to 2,326 days (mean (SD): 8.1 (15.9) days per participant) during the Study Period.

Secondary Endpoints

Time to First Exacerbation after Initiation of Tezepelumab

The Kaplan-Meier analysis evaluated the time to first asthma exacerbation in the FAS. Over the study period, the cumulative probability of experiencing a first asthma exacerbation gradually increased to approximately 0.44, indicating that approximately 56% of participants remained exacerbation-free by the end of the observation period.

Table 6. Time to first exacerbation after initiation of tezepelumab (FAS)

Overall

		Participants with events			Kaplan Meier estimate	
Timepoint	n	Number	(%)	Median time to event (days)	(%)	95 % CI
Visit 8 (6 months) N = 286	286	86	30.1	61	0.32	(0.26, 0.37)
Visit 15 (12 months) N = 286	286	120	42.0	102	0.44	(0.38, 0.50)

By Visit 15 (12 months), the proportion of participants experiencing a first asthma exacerbation among subgroups were:

- 36.0% (allergic with BEC <300 cells/μL)
- 39.5% (allergic with BEC ≥300 cells/μL)
- 42.2% (non-allergic with BEC ≥300 cells/μL)
- 50.0% (non-allergic with BEC <300 cells/μL)
- 36.8% (adolescents)
- 42.9% (Black/African American)
- 45.6% (comorbid diagnosis of mild to moderate COPD)

- 45.8% (smokers).

Asthma Exacerbations Resulting in Hospitalisations and Emergency Department/Urgent Care (ED/UC) Visits

In the overall population (N = 286), there was a substantial reduction in asthma exacerbations resulting in hospitalisation during the Study Period compared to the Baseline Period. During the 52-week Study Period, 10 events occurred yielding an adjusted rate of 0.0364 (95% CI: 0.02, 0.08) exacerbations per year. In contrast, the Baseline Period recorded 48 events with an adjusted rate of 0.1714 (95% CI: 0.12, 0.24) exacerbations per year. The rate ratio of 0.21 (95% CI: 0.09, 0.48) indicated a reduction in the annualised rate of asthma exacerbations resulting in hospitalisation during the Study Period compared to the Baseline Period.

Table 7. Rate of Asthma Exacerbations Resulting in Hospitalisation Visits in the Baseline and Study Period (FAS)

Overall

							Comparison with baseline period		
Period	n	Number of events	Total time at-risk	Crude rate	Adjusted rate	95% CI	Rate ratio	95% CI	p-value
Study Period, Visit 15 (12 months) N = 286	286	10	271.00	0.0369	0.0364	(0.02, 0.08)	0.21	(0.09, 0.48)	<0.001
Baseline Period (12 months) N = 286	286	48	282.74	0.1698	0.1714	(0.12, 0.24)			

In the overall population (N = 286), there was a substantial reduction in asthma exacerbations resulting in ED/UC visits during the Study Period compared to the Baseline Period. During the 52-week Study Period, 42 events occurred yielding an adjusted rate of 0.1568 (95% CI: 0.11, 0.23) exacerbations per year. In contrast, the Baseline Period recorded 178 events with an adjusted rate of 0.6771 (95% CI: 0.55, 0.84) exacerbations per year. The rate ratio of 0.23 (95% CI: 0.15, 0.35) indicated a reduction in the annualised rate of asthma exacerbations resulting in ED/UC visits during the Study Period compared to the Baseline Period.

Table 8. Rate of Asthma Exacerbations Resulting in ED/UC Visits in the Baseline and Study Period (FAS)

Overall

							Comparison with baseline period		
Period	n	Number of events	Total time at-risk	Crude rate	Adjusted rate	95% CI	Rate ratio	95% CI	p-value
Study Period, Visit 15 (12 months) N = 286	286	42	269.45	0.1559	0.1568	(0.11, 0.23)	0.23	(0.15, 0.35)	<0.001
Baseline Period (12 months) N = 286	286	178	275.51	0.6461	0.6771	(0.55, 0.84)			

The combined rate of asthma exacerbations resulting in hospitalisation or ED/UC visits (combined) showed a substantial reduction following tezepelumab treatment. In the overall population, the rate ratio was 0.24 (95% CI: 0.16, 0.36).

Additionally, the proportion of participants experiencing asthma exacerbations associated with hospitalisation or ED/UC visits decreased substantially from the Baseline Period to the Study Period:

- During the Baseline Period, 102 of 286 participants (35.7%) experienced at least one such severe exacerbation, with 36 participants (12.6%) requiring hospitalisation and 101 participants (35.3%) requiring ED/UC visits.
- During the Study Period, this proportion decreased to 34 of 286 participants (11.9%), with only 7 participants (2.4%) experiencing hospitalisations and 32 participants (11.2%) requiring ED/UC visits.

Reductions in hospitalisation and ED/UC visit rates were also observed across subgroups, with several subgroups, achieving zero hospitalisation events during the Study Period. Among participants with allergic asthma and BEC ≥300 cells/µL, the proportion with ED/UC visits decreased from 36.8% to 3.9%, with hospitalisations dropping from 11.8% to 0%. In Black/African American participants, the proportion with ED/UC visits decreased from 46.0% to 17.5%, and hospitalisations decreased from 25.4% to 1.6%. Adolescents showed complete elimination of such exacerbations, from 36.8% to 0% for ED/UC visits and from 21.1% to 0% for hospitalisations.

Pre-BD FEV1 and Change from Baseline in Pre-BD FEV1 at 6 and 12 Months After Initiation of Tezepelumab

The change from baseline in pre-BD FEV1 at 6- and 12-months following tezepelumab initiation was analyzed using a model for repeated measures. At 6 months (Visit 8), participants experienced a mean change from baseline of 0.108 L in pre-BD FEV1 (95% CI: 0.07, 0.15;). At 12 months, the LS mean change from baseline in pre-BD FEV1 was 0.122 L (95% CI: 0.07, 0.17). Among participants with baseline pre-BD FEV1 ≤80% predicted, the LS mean change was 0.212 L (95% CI: 0.15, 0.28) at 12 months.

At 12 months, subgroups showed variable responses. Black/African American participants experienced improvements (0.137 L [0.03, 0.24], n = 41). Adolescents showed improvements (0.283 L [–0.13, 0.70], n = 13). Smokers (≥10 pack-years) demonstrated modest improvements (0.114 L [0.01, 0.22], n = 61). Allergic participants with BEC ≥300 demonstrated substantial improvements (LS mean 0.266 L [95% CI: 0.16, 0.37], n = 56). Non-allergic participants with BEC ≥300 also showed improvements (0.199 L [0.11, 0.28], n = 39). In contrast, participants with BEC < 300 (both allergic and non-allergic) showed minimal changes.

Table 9. Pre-bronchodilator FEV1 Change from Baseline, Model for Repeated Measures (Full Analysis Set)

	Change from Baseline				
Timepoint	**n**	**LSMean**	**95% CI**	**SE**	**p-value**
Overall					
Visit 8 (6 months)	263	0.108	(0.07, 0.15)	0.02	< 0.001
Visit 15 (12 months)	222	0.122	(0.07, 0.17)	0.02	< 0.001
Baseline Pre-BD FEV1 (% Predicted) ≤ 80%					
Visit 8 (6 months)	165	0.179	(0.12, 0.23)	0.03	< 0.001
Visit 15 (12 months)	138	0.212	(0.15, 0.28)	0.03	< 0.001
Phase I: Allergic and BEC ≥ 300					
Visit 8 (6 months)	72	0.241	(0.15, 0.33)	0.05	< 0.001
Visit 15 (12 months)	56	0.266	(0.16, 0.37)	0.05	< 0.001
Phase I: Non-allergic and BEC ≥ 300					
Visit 8 (6 months)	43	0.196	(0.11, 0.28)	0.04	< 0.001
Visit 15 (12 months)	39	0.199	(0.11, 0.28)	0.04	< 0.001
Phase I: Allergic and BEC < 300					
Visit 8 (6 months)	80	0.015	(-0.06, 0.09)	0.04	0.7093
Visit 15 (12 months)	70	0.007	(-0.10, 0.11)	0.05	0.8989
Phase I: Non-allergic and BEC < 300					
Visit 8 (6 months)	66	0.023	(-0.04, 0.09)	0.03	0.4846
Visit 15 (12 months)	56	0.046	(-0.02, 0.11)	0.03	0.1553
Phase II: Black/African American					
Visit 8 (6 months)	53	0.144	(0.06, 0.23)	0.04	0.0017
Visit 15 (12 months)	41	0.137	(0.03, 0.24)	0.05	0.0116
Phase II: Adolescents					
Visit 8 (6 months)	18	0.199	(0.00, 0.40)	0.09	0.0493
Visit 15 (12 months)	13	0.283	(-0.13, 0.70)	0.17	0.1440
Phase II: Comorbid diagnosis of mild to moderate COPD					
Visit 8 (6 months)	52	0.057	(-0.04, 0.15)	0.05	0.2384
Visit 15 (12 months)	42	0.077	(-0.05, 0.21)	0.06	0.2401
Phase II: Smokers (history of ≥ 10 pack-years)					
Visit 8 (6 months)	76	0.075	(0.01, 0.14)	0.03	0.0284
Visit 15 (12 months)	61	0.114	(0.01, 0.22)	0.05	0.0330

Model: Estimate of the mean change from baseline at each timepoint after tezepelumab was obtained using a repeated measures analysis.
Estimates were least squares means. The model with unstructured matrix structure was: Change from baseline in pre-BD FEV1 = baseline pre-BD FEV1 + age + visit.
N = Number of participants in analysis

ACQ-6, AIRQ, and SGRQ at 6 and 12 Months After Initiation of Tezepelumab

ACQ-6:

- In the overall population, ACQ-6 scores decreased by an LS mean of -1.0898 (95% CI: -1.20, -0.98; n = 256; SE = 0.06) at 6 months and -1.2279 (95% CI: -1.35, -1.10; n = 219; SE = 0.06) at 12 months.

- In the overall population (N = 286), 180 participants (62.9%) were responders at 6 months, with 76 (26.6%) non-responders and 30 (10.5%) with missing data. At 12 months, 162 participants (56.6%) were responders, with 57 (19.9%) non-responders and 67 (23.4%) with missing data.
- At baseline, 57 participants (19.9%) had controlled asthma (ACQ-6 <1.5). By 6 months, the proportion with controlled asthma increased to 167 (58.4%), and at 12 months, 156 participants (54.5%) had controlled asthma.
- Improvements in asthma control status were observed across all subgroups.

AIRQ:

- In the overall population, AIRQ scores decreased by an LS mean of -2.8 (95% CI: -3.12, -2.56; n = 256) at 6 months and -2.9 (95% CI: -3.20, -2.60; n = 219) at 12 months.
- In the overall population (N = 286), 168 participants (58.7%) were responders at 6 months, with 88 (30.8%) non-responders and 30 (10.5%) with missing data. At 12 months, 139 participants (48.6%) were responders, with 80 (28.0%) non-responders and 67 (23.4%) with missing data.
- At baseline, 35 participants (12.2%) had well-controlled asthma (AIRQ = 0-1). By 6 months, the proportion with well-controlled asthma increased to 138 (48.3%), and at 12 months, 129 participants (45.1%) had well-controlled asthma.
- Improvements in asthma control status were observed across all subgroups.

SGRQ:

- In the overall population, SGRQ total scores decreased by an LS mean of -20.78 (95% CI: -23.00, -18.57; n = 256) at 6 months and - 22.1203 (95% CI: -24.71, -19.53; n = 219) at 12 months.
- In the overall population (N = 286), 207 participants (72.4%) were responders at 6 months, with 49 (17.1%) non-responders and 30 (10.5%) with missing data. At 12 months, 175 participants (61.2%) were responders, with 44 (15.4%) non-responders and 67 (23.4%) with missing data.

Systemic Corticosteroid Use

The proportion of participants requiring any SCS use decreased from 97.6% to 45.1%. The mean cumulative annualised SCS dose reduced from 3671.7 mg to 1283.8 mg, with an LS mean change of -535.121 mg (95% CI: -690.91, -379.33) at 12 months. 84.3% of participants achieved a reduction in SCS use. Reductions in SCS use were also observed across all subgroups.

Asthma-Related Healthcare Resource Utilization

The rate of asthma exacerbations resulting in hospitalisation decreased with a rate ratio of 0.21 (95% CI: 0.09, 0.48). The rate of asthma exacerbations resulting in ED/UC visits decreased with a rate ratio of 0.23 (95% CI: 0.15, 0.35). The proportion of participants with any asthma-related HRU decreased from 86.1%. to 58.2%.

Rapporteur's comments:

In the overall group, the adjusted AAER decreased from 2.8783 exacerbations per year during the Baseline Period to 0.8665 exacerbations per year in the Study Period. The rate ratio was 0.30 (95% CI: 0.25, 0.37), indicating a reduction in the AAER following treatment with tezepelumab.

Reductions in AAER were observed across all prespecified asthma phenotypes and underrepresented populations and across all subgroups, including adolescents, supporting the consistent efficacy of tezepelumab across diverse patient populations.

Evaluation of the cumulative probability of experiencing a first asthma exacerbation indicated that approximately 56% of participants remained exacerbation-free by the end of the Study Period. The probability of experiencing a first asthma exacerbation was lowest in the 'allergic with BEC <300 cells/µL' subgroup. This is consistent with the absence of key type 2 inflammatory drivers, including eosinophilia and allergic sensitisation in this subgroup, which are typically associated with increased exacerbation risk.

The lower probability of exacerbations observed in the adolescent subgroup (0.39), compared to the overall study population (0.44) may reflect the differing disease characteristics and shorter disease duration in this population, but the small number of adolescent participants in the study (n=19) limits interpretation of these findings.

Treatment with tezepelumab led to a significant reduction in the rate of asthma exacerbations resulting in hospitalisation or ED/UC visits and the proportion of participants experiencing asthma exacerbations associated with hospitalisations or ED/UC visits decreased substantially from the Baseline Period to the Study Period. This trend of reduction in severe exacerbations was consistent across subgroups, demonstrating consistent treatment effects across a broad range of patient populations.

Improvements in lung function were seen in the overall population and many of the subgroups. The greatest improvements were observed in participants with baseline FEV1 ≤80% predicted and those with allergic phenotype and BEC ≥300 cells/µL.

Asthma control was recorded through the use of three patient questionnaires: ACQ-6, AIRQ, and SGRQ. Between 48.6% and 61.2% of the overall population reported achieving clinically meaningful improvements at 12 months. Response rates varied across all subgroups, but overall results were robust across asthma phenotypes and underrepresented populations.

SCS use was greatly reduced in the Study Period compared with Baseline Period. Furthermore, reductions in the proportion of patients requiring any SCS use were observed across all subgroups, including in adolescents in which any SCS use decreased from 100.0% (19/19) during the Baseline Period to 42.1% (8/19) during the Study Period.

The proportion of participants with any asthma-related healthcare resource utilization, including healthcare visits, hospitalisations, and medical testing decreased between Baseline and Study Periods by 27.9 percentage points, further reflecting improved disease control during the Study Period.

Exploratory endpoints, which included analysis of patient's experience with tezepelumab, adherence/persistence, HRQoL, asthma trigger survey, clinical remission, total nasal symptom score, and sino-nasal outcome testing further supported the efficacy of tezepelumab with many patients reporting symptom improvements and enhanced HRQoL.

Safety results

The safety objective of this study was to describe the safety and tolerability of Tezepelumab and was based on evaluation of the following endpoints: occurrence of SAEs, AEs that lead to tezepelumab treatment discontinuation, and AESIs.

Extent of Exposure

The number of tezepelumab doses is summarized in the Table 10 below. In the overall population (N = 286), 80.4% of participants received all 13 planned doses. The proportion of participants receiving all 13 doses ranged from 68.3% to 86.7% across subgroups. Study intervention compliance was calculated as the ratio of actual dosing occasions to expected dosing occasions, multiplied by 100%. The mean (SD) compliance rate was 99.108% (3.381%), with a median of 100.0% (range: 69.23% to 100.0%). The majority of participants (285, 99.7%) achieved compliance between 75% and 100%, with mean compliance rates ranging from 97.670% to 99.595% across all subgroups.

Table 10. Number of Study Drug Doses (Full Analysis Set)

	Teze 210 mg Q4W
Overall	**N = 286** **n (%)**
Number of study intervention doses received	
13	230 (80.4)
12	20 (7.0)
11	6 (2.1)
10	2 (0.7)
9	2 (0.7)
8	3 (1.0)
7	5 (1.7)
6	4 (1.4)
5	3 (1.0)
3	4 (1.4)
2	4 (1.4)
1	3 (1.0)

The table presents number of participants having received the displayed number of doses. A participant was considered as having received a dose of study intervention on a given occasion, if they had received a full or partial dose. N = Number of participants; n = Number of participants per category.

Adverse Events

Safety and tolerability of tezepelumab were assessed from SAEs, SAEs with outcome of death, DAEs, AESIs, and laboratory tests.

Table 11. Overall Summary of Adverse Events On-treatment Period (Full Analysis Set)

	Teze 210 mg Q4W
Overall	**N = 286** **n (%)**
Any SAE	28 (9.8)
Any SAE with outcome of death	1 (0.3)
Any AE leading to study intervention discontinuation	6 (2.1)
Adults	**N = 267** **n (%)**
Any SAE	27 (10.1)
Any SAE with outcome of death	1 (0.4)
Any AE leading to study intervention discontinuation	6 (2.2)
Adolescents	**N = 19** **n (%)**
Any SAE	1 (5.3)

	Teze 210 mg Q4W
Any SAE with outcome of death	0
Any AE leading to study intervention discontinuation	0

The table includes AEs with an onset date on or after the date of first dose of study intervention up to and including 35 days following the date of last study intervention dose. The on-treatment period started on the index date and ended on earliest (date of last dose of study intervention + 35 days, date of death, date of study withdrawal). The date of study withdrawal was the completion or discontinuation date from the Disposition eCRF page, where any participant status other than "Completed" had been entered. Participants with multiple occurrences in the same category were counted once per category regardless of the number of occurrences.
N = Number of participants; n = Number of participants per category.

Adverse Events by System Organ Class and Preferred Term

All SAEs were assessed as not related to tezepelumab by investigators. However, the following notable events occurred during the study:

- Fatal Event: A patient experienced a myocardial infarction on Day 335, which resulted in death. The Investigator assessed this event as not related to tezepelumab, and study drug was withdrawn.
- Malignancies: Three participants were diagnosed with malignancies during the study, including lung neoplasm malignant (Day 119), breast cancer (Day 266), and squamous cell carcinoma (Day 21). All events were assessed as not related to tezepelumab by investigators.

Adverse Events of Special Interest

A total of 17 participants experienced 19 AESIs during the on-treatment period.

Key findings from the AESI analysis include:

- All AESIs were assessed by investigators as not related to the study intervention.
- One AESI resulted in death (myocardial infarction), with time from first study intervention to death of 335 days.

- The most frequent AESIs were pneumonia of various types (7 events), followed by malignancies including lung neoplasm malignant, squamous cell carcinoma, and breast cancer (3 events), sepsis/urosepsis (2 events), and tooth infection (1 event).

For this study, the following AESIs were included:

- Serious hypersensitivity reactions
- Serious infections
- Helminth infections (serious or non-serious)
- All malignancies (Note: all malignancies were considered 'serious' and reported as SAEs accordingly)
- Guillain Barre Syndrome (serious or non-serious)
- Serious cardiac events

No serious hypersensitivity reactions, no helminth infections (serious or non-serious), and no Guillain Barre syndrome (serious or non-serious) were reported in this study.

Serious Infections

Thirteen (4.5%) participants experienced at least one serious infection during the on-treatment period: pneumonia (4 participants [1.4%]), pneumonia bacterial (3 participants [1.0%]), and atypical pneumonia, COVID-19, COVID-19 pneumonia, pneumonia viral, respiratory syncytial virus infection, sepsis, tooth infection, and urosepsis (1 participant [0.3%] each). None of these AESIs were possibly related to the study intervention, as judged by the Investigator. All serious infections resolved.

Malignancies

Three participants (1.0%) experienced at least one malignancy during the on-treatment period: breast cancer, lung neoplasm malignant, and squamous cell carcinoma (1 participant [0.3%] each). None of these AEs were possibly related to the study intervention, as judged by the Investigator. Two malignancies resolved, and one (breast cancer) did not resolve till end of the study.

Serious Cardiac Events

One participant (0.3%) experienced a serious cardiac event during the on-treatment period: myocardial infarction. This AE was not possibly related to the study intervention, as judged by the Investigator. The event resulted in death.

Serious Adverse Events

During the on-treatment period, 28 participants (9.8%) had at least one SAE (including those with an outcome of death). The most frequently reported SAEs by SOC were Infections and infestations (13 participants [4.5%]), Respiratory, thoracic and mediastinal disorders (6 participants [2.1%]), and Nervous system disorders (4 participants [1.4%]). The most common (frequency of > 0.3%, i.e., more than 1 participant) SAEs by PT were asthma (5 participants [1.7%]), pneumonia (4 participants [1.4%]), and pneumonia bacterial (3 participants [1.0%]).

None of the 44 SAEs were considered related to study intervention by the Investigator. All SAEs resolved except for 3 events (1 fatal myocardial infarction, 1 breast cancer, and 1 case each of back pain and paraesthesia). Action taken with study intervention was 'dose not changed' for 33 SAEs, 'drug withdrawn' for 3 SAEs (including the fatal myocardial infarction), 'drug interrupted' for 1 SAE, and 'not applicable' for 7 SAEs.

One adolescent participant had an SAE of 'seizure' on Study Day 347. The most recent dose of study drug was given 9 days prior to the SAE at Visit 14. The patient was hospitalised and treated with diazepam nasal spray. There was no report of seizure in the patient's medical history, however there was a history of an unknown intracranial mass found in the brain in 2022. A paediatric neurology consultation determined that the seizure was generalized, with cyanosis, syncope, and post-ictal state. The patient was discharged from hospital on Study Day 348 as the SAE was resolved. The Investigator considered the SAE of seizure to be unrelated to study drug.

After Visit 15 (EOS), the patient received tezepelumab (not IP) and a second seizure occurred 4 days later. The patient attended the ER but was not hospitalised. A neurology follow-up noted autism-associated increased seizure risk, and attributed the seizure threshold changes to age, puberty, and sleep pattern shifts. MRI and CT imaging showed no acute findings, and an arachnoid cyst consistent with prior imaging. This event was not reported as an SAE as it was outside the Study Period.

Table 12. Serious Adverse Events On-treatment by System Organ Class and Preferred Term (Full Analysis Set)

	Teze 210 mg Q4W	
	N = 286	
System organ class	n (%)	n per 100
Preferred term		Participants years [a]
(MedDRA version 28.1)		
Any SAE	28 (9.8)	11.3
Infections and infestations	13 (4.5)	5.2
Atypical pneumonia	1 (0.3)	0.4
COVID-19	1 (0.3)	0.4
COVID-19 pneumonia	1 (0.3)	0.4
Pneumonia	4 (1.4)	1.6
Pneumonia bacterial	3 (1.0)	1.2
Pneumonia viral	1 (0.3)	0.4
Respiratory syncytial virus infection	1 (0.3)	0.4
Sepsis	1 (0.3)	0.4
Tooth infection	1 (0.3)	0.4
Urosepsis	1 (0.3)	0.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0)	1.2

Breast cancer	1 (0.3)	0.4
Lung neoplasm malignant	1 (0.3)	0.4
Squamous cell carcinoma	1 (0.3)	0.4
Metabolism and nutrition disorders	1 (0.3)	0.4
Lactic acidosis	1 (0.3)	0.4
Nervous system disorders	4 (1.4)	1.6
Cerebrovascular accident	1 (0.3)	0.4
Paraesthesia	1 (0.3)	0.4
Seizure	1 (0.3)	0.4
Transient ischaemic attack	1 (0.3)	0.4
Cardiac disorders	1 (0.3)	0.4
Myocardial infarction	1 (0.3)	0.4
Vascular disorders	1 (0.3)	0.4
Arterial occlusive disease	1 (0.3)	0.4
Respiratory, thoracic, and mediastinal disorders	6 (2.1)	2.4
Acute respiratory failure	1 (0.3)	0.4
Asthma	5 (1.7)	2.0
Pneumothorax	1 (0.3)	0.4
Pulmonary oedema	1 (0.3)	0.4
Gastrointestinal disorders	2 (0.7)	0.8
Abdominal hernia	1 (0.3)	0.4
Small intestinal obstruction	1 (0.3)	0.4
Hepatobiliary disorders	1 (0.3)	0.4
Cholecystitis acute	1 (0.3)	0.4
Musculoskeletal and connective tissue disorders	2 (0.7)	0.8
Arthritis	1 (0.3)	0.4
Back pain	1 (0.3)	0.4
Renal and urinary disorders	1 (0.3)	0.4
Acute kidney injury	1 (0.3)	0.4
General disorders and administration site conditions	2 (0.7)	0.8
Non-cardiac chest pain	2 (0.7)	0.8

a Number of participants with an AE divided by the total number of days at risk for AEs across all participants multiplied by 365.25 multiplied by 100.
The table includes AEs with an onset date on or after the date of first dose of study intervention until the final follow-up visit. Participants with multiple occurrences in the same category were counted once per category regardless of the number of occurrences. Table was sorted by international order for SOC and in alphabetical order for preferred term. The on-treatment period started on the index date and ended on earliest (date of last dose of study intervention + 35 days, date of death, date of
study withdrawal). The date of study withdrawal was the completion or discontinuation date from the Disposition eCRF page, where any participant status other than "Completed" had been entered.

N = Number of participants per treatment group; n = Number of participants per category.

Discontinuations of Investigational Medicinal Product Due to Adverse Events

Six participants (2.1%) reported an AE leading to discontinuation of study intervention. The AEs leading to discontinuation were breast cancer, syncope, myocardial infarction, asthma, alopecia, and rash erythematous (1 participant [0.3%] each). Of note, 3 of the AEs leading to discontinuation (myocardial infarction, asthma, and breast cancer) were SAEs, with myocardial infarction resulting in death.

Only one AE leading to discontinuation (rash erythematous) was assessed as possibly related to study intervention by the Investigator. This event did not resolve. Of the remaining AEs, 2 resolved (asthma and syncope), 2 did not resolve (breast cancer and alopecia), and 1 was fatal (myocardial infarction).

Table 13. Adverse Events On-treatment Leading to Discontinuation of Investigational Product by System Organ Class and Preferred Term (Full Analysis Set)

System organ class	Teze 210 mg Q4W
Preferred term	N = 286
(MedDRA version 28.1)	n (%)
Any AE leading to study intervention discontinuation	6 (2.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)
Breast cancer	1 (0.3)
Nervous system disorders	1 (0.3)
Syncope	1 (0.3)
Cardiac disorders	1 (0.3)
Myocardial infarction	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.3)
Asthma	1 (0.3)
Skin and subcutaneous tissue disorders	2 (0.7)
Alopecia	1 (0.3)
Rash erythematous	1 (0.3)

The table includes AEs with an onset date on or after the date of first dose of study intervention until the final follow-up visit.
Participants with multiple occurrences in the same category were counted once per category regardless of the number of occurrences. Table was sorted by international order for SOC and in alphabetical order for PT. The on-treatment period started on the index date and ended on earliest (date of last dose of study intervention + 35 days, date of death, date of study withdrawal). The date of study withdrawal was the completion or discontinuation date from the Disposition eCRF page, where any participant status other than "Completed" had been entered

N = Number of participants per treatment group; n = Number of participants per category.

Deaths

In the on-treatment period, 1 (0.3%) participant had an SAE with an outcome of death. The death was not considered related to study intervention. In the on-study period, one participant died. The participants who died are described below, with relevant data and the Investigator's opinion on the likelihood of a causal relationship between death and study treatment.

A patient, who had medical history that included hypercholesterolaemia, tachyarrhythmia, and coronary artery disease, experienced a myocardial infarction on Day 335 of the study. The event occurred 28 days after the latest dose of study intervention. Death occurred on Day 335 from first

dose of study intervention. Myocardial infarction was reported as the fatal AE, and this event was assessed as not related to study intervention by the Investigator. Study drug had been withdrawn prior to the fatal outcome.

A patient experienced COVID-19 pneumonia on Day 179 of the study and hospitalised. The event was resolved on Day 209 of the study. Death occurred on Day 215 of study due to natural cause. COVID-19 pneumonia and death both assessed as not related to study intervention by the Investigator.

Clinical Laboratory Evaluation

In this study, haematology and chemistry assessments were performed at screening only. Participants treated with tezepelumab showed reductions in inflammatory biomarkers from baseline, including blood eosinophil count, total immunoglobulin E and perennial aeroallergen-specific immunoglobulin E.

The mean (SD) change from baseline to week 52 in BEC was -0.141 (0.286) 109/L and in total IgE level was -73.788 (339.740) IU/mL.

Vital Signs, Electrocardiograms, Physical Findings and Other Observations Related to Safety

Mean weight, height, and BMI over time were recorded. There were no clinically significant changes from baseline in mean weight and mean BMI.

Rapporteur's comments

In the overall population (N = 286) comprising 267 adults and 19 adolescents, 80.4% of participants received all 13 planned doses. The proportion of participants receiving all 13 doses ranged from 68.3% to 86.7% across subgroups. The mean (SD) treatment compliance was 99.1% (3.4%), with 80.4% of participants receiving all 13 planned doses of tezepelumab 210 mg Q4W. This high compliance supports the credibility of the study findings regarding real world effectiveness, while also indicating good patient acceptability.

In this study, serious adverse events occurred in a small proportion of participants, affecting 10.1% of adults (including one death 'on treatment' and one death considered to be 'off treatment' and 2.2% treatment discontinuation) and 5.3% of adolescents, with no deaths or treatment discontinuations reported in the younger group.

Overall, during the on-treatment period, 28 (9.8%) participants reported 44 SAEs, with 1 (0.3%) participant had an SAE with an outcome of death (Myocardial infarction) 28 days after the latest dose of study intervention. The death was not assessed as being related to study intervention by the Investigator. One other patient had an SAE with an outcome of death (COVID-19 pneumonia that resolved followed by death by natural causes 6 days later). This death was also not assessed as being related to study intervention by the Investigator. All SAEs of the other were considered as not related to tezepelumab by the Investigator. Serious adverse events were reported at similar rates to the pivotal trials, with no evidence of an increase in overall SAE risk.

One adolescent patient reported an SAE of seizure which was not considered related to study medication. This occurred 9 days following study treatment. After Visit 15 (EOS), the patient received tezepelumab (not IP) and a second seizure occurred 4 days later. The patient attended the ER but was not hospitalised. A neurology follow-up noted autism-associated increased seizure risk, and attributed the seizure threshold changes to age, puberty, and sleep pattern shifts. This patient also had a history of stable left middle cranial fossa arachnoid cyst. MRI and CT imaging showed no acute findings, and an arachnoid cyst consistent with prior imaging. This event was not reported as an SAE as it was outside the Study Period. These events are confounded by the patients past medical history of autism and left middle cranial fossa arachnoid cyst.

A subsequent, comprehensive review of seizure-related AEs was conducted through the pooled data from tezepelumab studies (Phase II studies PATHWAY and CASCADE; Phase III studies: NAVIGATOR, SOURCE, DESTINATION, PATH-HOME, NOZOMI, VECTOR, WAYPOINT, SUNRISE, and DIRECTION). The pooled analysis included all participants who received at least one dose of tezepelumab or placebo.

There were 1734 adult participants who received tezepelumab 210 mg Q4W (including those originally receiving placebo and re-randomized to receive tezepelumab in the DESTINATION LTE study). Overall, incidence rates of seizure events were low and comparable between the tezepelumab and placebo groups in the pooled dataset for both overall (0.12 vs 0.39 per 100 subject-years) and serious events (0.06 vs 0.15 per 100 subject-years). Two participants reported an AE related to seizure in the pooled tezepelumab-treated population (PTs of partial seizures and psychogenic seizures). The psychogenic seizure event was considered an SAE by the Investigator. Five patients in the pooled placebo group reported AEs related to seizure, two of which were considered SAEs.

Adolescents (Age: ≥12 to <18 years) were among those enrolled in the NAVIGATOR, DESTINATION, PATH-HOME, NOZOMI, and VECTOR studies. No seizure-related event was reported in the adolescent population across all the pooled tezepelumab studies.

There is no established pharmacological basis by which inhibition of TSLP signalling would be expected to lower seizure threshold or directly affect central nervous system excitability. In addition, tezepelumab does not cross the blood-brain barrier, and no effects on CNS-related biomarkers have been identified in preclinical or clinical studies. Thus, the biological plausibility of a causal relationship between tezepelumab and seizure events is considered low.

Discontinuation rates were low. Five out of 6 AEs resulting in discontinuation were considered as not related to tezepelumab by the Investigator. One participant experienced an AE that was assessed by the Investigator as possibly related to study intervention (rash erythematous). Rash is listed as a common ADR under the Skin and Subcutaneous SOC in section 4.8 of the SmPC for Tezspire.

An overview of safety for the other underrepresented subgroups Black/African American participants, participants with comorbid mild to moderate COPD, and smokers with ≥10 pack-year history have not been presented as part of this submission. As these data are being reviewed in the context of an Art 46 procedure, and the number of adolescents in these subgroups is likely to be very small these data are not being further pursued.

The percentage of patients reporting AESIs was low. The AESIs reported during the study (serious infections (13 participants [4.5%]), malignancies (3 participants [1.0%]), and serious cardiac events (1 participant [0.3%]). None of these AESIs were considered as related to Tezepelumab by the Investigator. No meaningful increase in serious infection risk was identified. The 4.5% rate is within the expected range for a severe asthma population and consistent with the original pivotal trial data. A malignancy rate of 1.0% is consistent with background incidence and does not suggest an emerging signal. The very low frequency (0.3%) of serious cardiac events is in line with expectations and does not indicate a treatment-related risk. Overall, the pattern and frequency of AESIs observed in this study were consistent with the known safety profile of tezepelumab, and no new safety signals or unexpected findings were identified. Of note serious infections, serious cardiac events and malignancy are included as important potential risks in the RMP for Tezspire. Serious Cardiac Events are being evaluated in Post-authorisation Safety Study (D5180R00024). The known risks of Serious infections and serious cardiac events are further mitigated through SmPC wording in section 4.4 and in the PIL.

Overall, the safety profile of tezepelumab was consistent with previous studies and showed no indication of new or increased safety signals in the studied adult or adolescent populations with severe asthma.

Discussion on clinical aspects

Tezepelumab (TEZSPIRE®) was approved in the EU in 2022 as an add-on maintenance treatment in patients 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids. In 2025, tezepelumab was approved in the EU as an add-on maintenance treatment for adult patients with CRSwNP and in the US for adult and paediatric patients aged 12 years and older. Currently, tezepelumab is approved in 70 countries for the treatment of asthma and more than 40 countries for the treatment of CRSwNP.

The MAH has submitted the final study report for Study D5180C00032 (PASSAGE). Data from this multicentre, single-arm, open-label, post-authorisation, Phase 4 evaluates the effectiveness and safety of tezepelumab in adult and adolescent participants with severe asthma including several under-studied populations in the US.

The primary objective of Study D5180C00032 was to assess the effectiveness of tezepelumab in the US in a broad population of participants with severe uncontrolled asthma across traditional asthma phenotypes of high and low blood eosinophils and allergic status as well as four eligible but under-studied populations: individuals who identified as Black/African American, adolescents (12 to 17 years), those with a comorbid diagnosis of mild to moderate COPD, and those with significant smoking history (≥10 pack-years of smoking).

Adolescent patients with severe asthma currently have access to tezepelumab as per the indication, however data in this population is limited. It is noted in the SmPC that a total of 82 adolescents aged 12 to 17 with severe, uncontrolled asthma were enrolled in the 52-week Phase 3 NAVIGATOR study, with 41 of those patients receiving treatment with tezepelumab. Study D5180C00032 provides open-label safety and efficacy data on a further 19 adolescent patients aged 12-17 years. Tezepelumab has not been studied in children under 12 years of age for the treatment of asthma or in children under 18 years of age for the treatment of CRSwNP.

This study is not included in the PIP and is submitted as a stand-alone Article 46 submission in accordance with the requirements of the Paediatric Regulation.

Efficacy

The purpose of this study was to assess the effectiveness and safety of tezepelumab in a diverse, real-world population of US patients with severe asthma. The study enrolled 286 participants and had high treatment and study completion rates. Overall, the study population was representative of the target population, including by asthma phenotypes and under-represented populations, although the number of adolescent participants was limited.

The study was an open-label, single-arm design which limits the ability to definitively attribute the observed outcomes to tezepelumab, however it does contribute to the overall understanding of its effectiveness and safety in routine clinical practice. Substantial reductions in AAERs were seen across the overall study population and subgroups, along with clinically meaningful improvements in lung function, asthma control, and health-related quality of life.

The results were generally consistent across all demographic and clinical subgroups, including asthma phenotypes (allergic and non-allergic asthma across varying blood eosinophil levels), adolescents,

Black/African American participants, those with comorbid COPD, and participants with a significant smoking history. This supports the generalisability of clinical findings across diverse patient populations and indicates that treatment benefits are widely applicable.

Safety

In the overall population (N = 286) comprising 267 adults and 19 adolescents, 80.4% of participants received all 13 planned doses. The proportion of participants receiving all 13 doses ranged from 68.3% to 86.7% across subgroups. The mean treatment compliance was 99.1% with 80.4% of participants receiving all 13 planned doses of tezepelumab 210 mg Q4W. This high compliance supports the credibility of the study findings regarding real world effectiveness, while also indicating good patient acceptability.

Across the whole study population, there were 44 SAEs reported during the 'on treatment' period, 1 with a fatal outcome in an adult patient (not considered related to treatment). The CSR states that the fatal event of MI was reported in a patient experienced a myocardial infarction on Day 335, which resulted in death. The Investigator assessed this event as not related to tezepelumab, and study drug was withdrawn. There was one further death reported in a patient 47 days after last study treatment. This was considered to be off treatment as it was greater than 35 days since last study treatment. The participant experienced COVID-19 pneumonia that resolved followed by death by natural causes 6 days later. This death was also assessed as not being related to study intervention by the Investigator.

Study discontinuation rates due to an AE were low. Five out of a total of 6 AEs resulting in discontinuation were considered as not related to tezepelumab by the Investigator. One participant experienced an AE that was assessed by the Investigator as possibly related to study intervention (rash erythematous). Rash is listed as a common ADR under the Skin and Subcutaneous SOC in section 4.8 of the SmPC for Tezspire.

There were no SAEs resulting in death or AEs leading to discontinuation of study intervention in the adolescent population.

The percentage of patients in the overall study population reporting AESIs was low. The AESIs reported during the study (serious infections (13 participants [4.5%]), malignancies (3 participants [1.0%]), and serious cardiac events (1 participant [0.3%]). None of these AESIs were considered as related to tezepelumab by the Investigator. Of note there were no AESIs reported in the adolescent subgroup. No meaningful increase in serious infection risk was identified. The 4.5% rate is within the expected range for a severe asthma population and consistent with the original pivotal trial data. A malignancy rate of 1.0% is consistent with background incidence and does not suggest an emerging signal. The very low frequency (0.3%) of serious cardiac events is in line with expectations and does not indicate a treatment-related risk. Overall, the pattern and frequency of AESIs observed in this study were consistent with the known safety profile of tezepelumab, and no new safety signals or unexpected findings were identified. Of note serious infections, serious cardiac events and malignancy are included as important potential risks in the RMP for Tezspire. Serious Cardiac Events are being evaluated in Post-authorisation Safety Study(D5180R00024). The known risks of Serious infections and serious cardiac events are further mitigated through SmPC wording in section 4.4 and in the PIL. Safety topics of special interest should continue to be presented and discussed in the PSURs (malignancies, serious infections, serious cardiac events).

One SAE of seizure was reported in an adolescent. Although a temporal association with tezepelumab was noted, a definitive causal relationship could not be established given the confounding effect of the patient's pre-existing medical history. Furthermore, a review of pooled tezepelumab clinical trial data demonstrated that the incidence of seizure-related AEs was low and comparable between the tezepelumab and placebo groups in adults, with no seizure-related AEs reported among adolescents

treated with tezepelumab. Finally, given the absence of a biologically plausible mechanism through which tezepelumab could precipitate seizure activity, the observed events are considered unlikely to reflect a causal effect of the drug. Monitoring of seizure-related events through routine pharmacovigilance activities is therefore considered acceptable.

Overall, the safety profile of tezepelumab was consistent with previous studies and showed no indication of new or increased safety signals in the studied adult or adolescent populations with severe asthma.

It is agreed that no updates to the PI are required from a safety perspective based on the limited data provided.

3. Rapporteur's overall conclusion and recommendation

In the context of this PAM for a completed study involving adolescent participants for Tezspire (tezepelumab) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, the MAH has met their obligations.

The study was an open-label, single-arm design which limits the ability to definitively attribute the observed outcomes to tezepelumab; however, it does contribute to the overall understanding of its effectiveness and safety in routine clinical practice. Substantial reductions in AAERs were seen across the overall study population and subgroups, along with clinically meaningful improvements in lung function, asthma control, and health-related quality of life. Overall, although the data set is too limited to draw robust conclusions, the safety profile for the adults and adolescents from this study are generally consistent with known safety profile for tezepelumab.

The Rapporteur considers that the requirements of the Article 46 for Tezspire have been fulfilled. Based on the results of Study D5180C00032, it is agreed that the benefit-risk profile for tezepelumab remains the same and no update to the product information is deemed necessary.

☒ **Fulfilled:**

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. One SAE of seizure followed by a second seizure post EOS in an adolescent is confounded by past medical history but a temporal association with treatment with tezepelumab is noted in both cases. The MAH is asked to monitor reports of seizures in adolescent population in future PSURs. **(OC)**

The timetable is a 30-day response timetable without clock stop.

5. Assessment of MAH responses to Request for supplementary information

Question 1

One SAE of seizure followed by a second seizure post EOS in an adolescent is confounded by past medical history but a temporal association with treatment with tezepelumab is noted in both cases. The MAH is asked to monitor reports of seizures in adolescent population in future PSURs. **(OC)**

Assessment of MAH response

The MAH provided further analysis of the reported seizure case from the PASSAGE study. Although a temporal association with tezepelumab was noted, it is agreed that a definitive causal relationship could not be established given the patient's underlying medical history.

The MAH also conducted a comprehensive review of pooled tezepelumab clinical trial data which demonstrated that the incidence of seizure-related AEs was low and comparable between the tezepelumab and placebo groups in adults, with no seizure-related AEs reported among adolescents treated with tezepelumab. Finally, based on available scientific and pharmacological evidence, the MAH assessed the biological plausibility of tezepelumab-induced seizure events as low, concluding that conclusion that the observed events are unlikely to represent a drug-related effect.

Based on the totality of the data presented by the MAH, it is agreed that the likelihood of a causal association between tezepelumab and seizure-related AEs is low, and therefore monitoring of seizure-related events through routine surveillance activities is considered acceptable.