Cover page

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

Sponsor Name: AstraZeneca AB, 151 85 Södertälje

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Regulatory Agency Identifier Number(s)

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: 3.0

Amendment Number: 2

Study Intervention: Tezepelumab

Study Phase: IV

Short Title: A single-arm, open-label, Phase 4 effectiveness and safety study of tezepelumab in adults and adolescent participants with severe asthma in the United States

Acronym: PASSAGE

Study Physician Name and Contact Information will be provided separately

Principal Investigator: Dr. Njira Lugogo. University of Michigan Health. Michigan, USA

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2, Version 3.0	12-Jan-2023
Amendment 1, Version 2.0	24-Jan-2022
Version 1.0	16-Nov-2021

Amendment 2 12 January 2023

Overall rationale for the Amendment

The Clinical Study Protocol (CSP) version 2.0, dated 24-Jan-2022, has been amended to update and clarify objectives and endpoints, Schedule of Activities and statistical analysis, to delete one inclusion criterion, to add details on medical device deficiencies and reporting requirements, and to provide further clarifications that are listed in the below table. Additionally, minor typographical and formatting updates have been made throughout.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
General	The term 'IP' is replaced by the term 'study intervention'.	Tezepelumab is an approved product.	Non-substantial
Section 1.1 Synopsis; Section 3 Objectives and Endpoints; Section 9.4.2 Efficacy; Section 8.1.1 Assessment of Asthma Exacerbation	Specified time period of 52 weeks for all the endpoints. Also, for these endpoints, the terms 'baseline period' and 'study period' were added to indicate the periods which are 52 weeks (or 12 months) before and after initiation of tezepelumab respectively.	For clarification.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Section 1.1 Synopsis; Section 3 Objectives and Endpoints; Section 9.4.2.1 Primary Endpoint(s)	Specified the estimand description including supportive endpoints for the primary objective.	For clarification.	Non-substantial
Section 1.1 Synopsis; Section 3 Objectives and Endpoints; Section 9.4.2.2 Secondary Endpoint(s)	Updated the endpoint description associated with the secondary objectives related to asthma exacerbation and asthma-related healthcare resource utilization (HRU) in subgroup of participants and asthma exacerbations resulting in hospitalizations or emergency department/urgent care (ED/UC) visits.	For clarification.	Non-substantial
	Removed the endpoints (annualized rate of ED/UC visits and hospitalizations) related to the secondary objective on asthma-related healthcare resource utilization (HRU).	These endpoints are covered within secondary and exploratory objectives related to asthma exacerbations and asthma-related HRU in subgroup of participants.	Non-substantial
	Added new secondary objective ‘To describe the time to first exacerbation after initiation of tezepelumab’.	For alignment with the development program.	Non-substantial
	Updated the text ‘a’ with ‘at least’ in the definition of pre-BD FEV1 responders to include participants who achieve either at least 5 % or 100 mL improvement from baseline.	For clarification.	Not substantial
Section 1.1 Synopsis; Section 4.1 Overall Design	Clarified monitoring and closure of subgroups.	For flexibility and clarification that targets are not commitments.	Non-substantial
Section 4.1 Overall Design	Updated text ‘nasal polyps’ with the text ‘Chronic Rhinosinusitis with nasal polyps’ in the sentence regarding participants with this comorbid condition and their enrolment.	For clarification.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Section 1.1 Synopsis; Section 9.4.2.1 Primary Endpoint(s)	Updated annual exacerbation rate derivation.	For clarification.	Non-substantial
Section 1.3 Schedule of Activities	Clarified footnote 'e' regarding assessment of spirometry in relation to the pre- and post-tezepelumab dosing.	For clarification.	Non-substantial
Section 1.3 Schedule of Activities; Section 8.2 Asthma Clinical Remission	Clinical remission assessment is removed from the Schedule of Activities (Section 1.3). The defining variables for asthma clinical remission are updated and the reference 'Lommatzsch et al., 2022' is cited in Section 8.2.	Clarified the asthma clinical remission criteria. As the clinical remission is not an assessment, it was deleted from the Schedule of Activities.	Non-substantial
Section 1.3 Schedule of Activities; Section 8.5.2 Vital Signs	Weight and height added to the Schedule of Activities.	For alignment with the development program.	Non-substantial
Section 1.3 Schedule of Activities; Section 8.1.1 Assessment of Asthma Exacerbation; Section 8.1.2 Assessment of SCS Use; Section 8.3 Healthcare Resource Utilization (HRU)	Assessments of asthma exacerbations, SCS use and HRU will be done at Visit 1 (and Visit 2 if performed separately).	For clarification.	Non-substantial
Section 1.3 Schedule of Activities; Section 8.1.4.8 SNOT-22	The text related to assessment of SNOT-22 for participants with 'symptoms of rhinosinusitis' has been updated to 'ongoing diagnosis of chronic rhinosinusitis with or without nasal polyps (defined as an ongoing history of 'Rhinitis,' 'Chronic Sinusitis,' and/or 'Nasal Polyps' on the Respiratory Medical History eCRF) at baseline, regardless of whether symptoms are present on the day of Visit 1 or 2.	For clarification and alignment with eCRF.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Section 3 Objectives and Endpoints; Section 9.4.2.3 Exploratory Endpoint(s)	Updated exploratory endpoints related to exploratory objective on asthma exacerbations and asthma-related HRU in a sample permitting for exploratory subgroup of participants. It was specified that exploratory subgroups of participants will be defined in the SAP.	For clarification and alignment with the changes made to the endpoints of the secondary objective (related to asthma exacerbations and asthma-related HRU in exploratory subgroup of participants).	Non-substantial
Section 5.1 Inclusion Criteria	Removed inclusion criterion related to the requirement to complete the full course of COVID-19 vaccination at least 28 days prior to the administration of tezepelumab.	Vaccination requirement is no longer justified. This will remove barriers and bias for recruitment.	Non-substantial
Section 5.4.1 Re-screening	Updated ICF signing requirements for re-screened participants.	To reduce the inconvenience for participants who are re-screened.	Non-substantial
Section 6.2.6 Single Use APFS Device Malfunction	Modified the reporting of device malfunctions in paper form (AstraZeneca Product Complaint Intake form) instead of eCRF.	Device malfunctions are not to be reported in the eCRF, but rather a paper form is to be used.	Non-substantial
Section 6.2.6 Single use APFS Device Malfuntion, Section 8.6.13 Medical Device Deficiencies Appendix F Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies	Added text in Section 6.2.6 mentioning that device malfunctions will be reported using AstraZeneca Product Complaint Intake form and added reference to Appendix F. Added text on medical device deficiencies in Section 8.6.13 including reporting requirements. Appendix F contains information on medical device AE, ADE, SAE, SADE, USADE, medical device deficiency, assessments of causality, intensity and reporting requirements.	For clarification of the process to be followed in case of medical device AEs, SAEs and deficiencies.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Section 8.1.1 Assessment of Asthma Exacerbations	Deletion of text related to participants receiving a stable maintenance dose of OCS.	For alignment with the AstraZeneca guidelines.	Non-substantial
	Removed reference to completing the eCRF in a timely fashion.	To remove a contradiction.	Non-substantial
Section 8.1.3 Spirometry	Deleted the text 'if captured in the EDC system'.	Date, time and results of spirometry are captured in EDC.	Non-substantial
Section 8.1.4 Clinical Outcome Assessments (COAs)	Added statement that paper questionnaires are not allowed in the study.	For clarification.	Non-substantial
Section 8.1.4.1 Asthma Control Questionnaire 6 (ACQ-6)	Removed reference to MCID being defined in the SAP.	To decrease redundant information.	Non-substantial
Section 1.3 Schedule of Activities; Section 3 Objectives and Endpoints, Section 8.1.4.10 Patient's Global Impression of Change (PGI-C), Section 9.4.2.3 Exploratory Endpoint(s)	Updated text that only those participants with ongoing diagnosis of COPD prior to tezepelumab dosing at Visit 2 will be asked to complete PGI-C.	For clarification and alignment with eCRF.	Non-substantial
Section 8.3 Healthcare Resource Utilization (HRU)	Deleted the sub-bulleted information on any HRU associated with asthma exacerbation (emergency department visits, inpatient hospitalization, unscheduled HCP visits, exacerbation related to SCS and antibiotic courses).	For alignment with the development program.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Section 1.3 Schedule of Activities, Section 8.5.4 Other Clinical Tests of Interests	Added Section 8.5.4 to explain that 'X-ray, CT scan, and/or FeNO' assessments performed as per routine clinical practice will be collected retrospectively at 12 months prior to Visit 2 and 6 months prior to Visit 8 and at Visit 15. This information is reflected in Section 1.3.	For clarification.	Non-substantial
Section 8.6.2 Follow-up of AEs and SAEs	Added 'maximum intensity' as one of the variables for SAE, DAE, and AESI collection.	For alignment with the development program.	Non-substantial
Section 8.6.6 Adverse Events of Special Interest	Added 'serious cardiac events' as one of the AESIs for tezepelumab.	For alignment with the updated Investigator Brochure.	Non-substantial
	Updated AESI definition and reporting requirements.		
	Deleted 'including serious opportunistic infection' for the category 'Serious infections'.		
	Added "serious or non-serious" to Helminth infections and Guillain Barre Syndrome.		
Section 9.4.1 General Considerations	Added general clarification on data to be included in statistical analysis.	For clarification.	Non-substantial
Section 1.1 Synopsis; Section 8.1.1 Assessment of Asthma Exacerbations; Section 9.4.2.1 Primary Endpoint(s)	Removed definition of relapse of asthma exacerbation in Section 8.1.1 and added an updated definition in Section 1.1 and Section 9.4.2.1.	For alignment with the AstraZeneca standards related to asthma exacerbations.	Non-substantial
Section 9.4.2.1 Primary Endpoint(s)	Updated description and the methods of analysis of primary endpoint.	For clarification.	Non-substantial
Section 9.4.2.2 Secondary Endpoint(s)	The list of secondary endpoints and the analyses has been updated to be consistent with objectives in Section 1.1and Section 3.	For clarification.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Section 9.4.2.3 Exploratory Endpoint(s)	The list of exploratory endpoints and analyses have been updated to be consistent with the objectives in Section 3.	For clarification.	Non-substantial
	Removed reference to correlation between baseline value and change from baseline.	Not relevant to study analyses.	Non-substantial
Section 9.4.3 Safety	Clarified MedDRA version and use of WHO Drug Dictionary for the classification of medications.	For clarification.	Non-substantial
	Updated analysis of SAEs, DAEs and AESIs to include summarization of these events during the on-treatment and on-study periods and by causality/relatedness and maximum intensity.	For alignment with the development program.	Non-substantial
	Added analysis methods for laboratory data.	For consistency of reporting.	Non-substantial
Section 9.5 Interim Analyses	Updated interim analysis text as follows: • to remove specific timings • to explain the rationale for interim analysis • to explain that the results of the interim analysis will not result in study design changes.	For flexibility.	Non-substantial
Appendix D Maintentance Therapy Equivalence Table (medium, and high daily dosage of inhaled corticosteroids)	Updated table to add additional maintenance therapy options and update total daily doses.	The original table in the protocol did not place a lower bound on medium-dose ICS. The updates better support investigator decision-making on the eligibility criteria related to ICS.	Non-substantial
Appendix H TEZSPIRE™ USPI	Added text that this is the current USPI at the time of protocol finalization.	For clarification.	Non-substantial

Abbreviations: ACQ = Asthma Control Questionnaire 6; ADE = adverse device effect; AESI = adverse event of special interest; APFS = accessorized pre-filled syringes; COVID-19 = Coronavirus disease of 2019; CT = computed tomography; DAE = Adverse event leading to discontinuation of tezepelumab; eCRF = electronic case report form; ED = Emergency Department; FeNO = Fractional Exhaled Nitric Oxide; ICF = informed consent form; ICS = inhaled corticosteroids; MCID = Minimum clinically important difference; OCS = oral corticosteroids; MedDRA = Medical Dictionary for Regulatory Activities; SADE = serious adverse device effect; SAE = serious adverse event; SAP = Statistical Analysis Plan; SNOT-22 = Sino-nasal Outcome Test; USADE = unanticipated serious adverse device effect; WHO = World Health Organization

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1 PROTOCOL SUMMARY

1.1 Synopsis

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

Short Title: A single-arm, open-label, Phase 4 effectiveness and safety study of tezepelumab in adults and adolescent participants with severe asthma in the United States (PASSAGE).

Rationale: The purpose of PASSAGE is to assess the effectiveness of tezepelumab in the United States (US) among a real-world population of adults and adolescent participants with asthma requiring medium-dose to high-dose inhaled corticosteroids (ICS), with additional controller(s) for at least 12 months prior to Visit 1, and with a documented history of at least 2 asthma exacerbations in the prior year. The study population will include 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 (aged 12-17 years), those with a comorbid diagnosis of mild to moderate chronic obstructive pulmonary disease (COPD) consistent with Global Initiative For Chronic Obstructive Lung Disease (GOLD) guidelines (2021), and those with a significant smoking history (≥10 pack-years of smoking). Participants will receive tezepelumab on an open-label basis. Participants will receive a standard dosing regimen of tezepelumab as per the current approved United States Prescribing Information (USPI), which is 210 mg dose Q4W.

Objectives and Endpoints

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** • Annualized asthma exacerbation rate (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

Objectives	Estimand description/Endpoints
	• 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 inhaled corticosteroids (ICS), requiring additional controller(s), and those with at least 2 asthma exacerbations in the prior year who received at least one dose of tezepelumab
	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).
	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, emergency department/urgent care (ED/UC) visits in the 12-month periods before (baseline period) and after initiation of tezepelumab (study period)	• Rate of asthma exacerbations associated with hospitalization 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) • 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 exacerbation days associated with hospitalizations or ED/UC

Objectives	Estimand description/Endpoints
	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-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV_1) • Change from baseline in pre-BD FEV_1 • Proportion of pre-BD FEV_1 responders (defined as participants who achieve either at least 5% or 100 mL improvement from baseline)
To describe Asthma Control Questionnaire (ACQ-6), Asthma Impairment and Risk Questionnaire (AIRQ), and St. George's Respiratory Questionnaire (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])
To describe systemic corticosteroid (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 healthcare resource utilization (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: • Blood eosinophil count (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)	• AAER over 52 weeks before (baseline period) and after initiation of tezepelumab (study period) • 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 of total number of asthma exacerbations • Cumulative asthma exacerbation days over 52 weeks before (baseline period) and after initiation of tezepelumab (study period)

Objectives	Estimand description/Endpoints
• Comorbid diagnosis of mild to moderate chronic obstructive pulmonary disease (COPD)[d] • Significant smoking history (≥10 pack-years of smoking)	• 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 Objective	
To describe the safety and tolerability of tezepelumab	• Occurrence of serious adverse events, adverse events that lead to tezepelumab treatment discontinuation, and adverse events of special interest

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

[b] Minimum clinically important difference (MCID) will be defined in the Statistical Analysis Plan (SAP).

[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 Fluorescent Enzyme Immunoassay (FEIA) at baseline.

[d] Consistent with GOLD 2021 guidelines.

For exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design

This is a multicenter, single-arm, open-label, post-authorization, Phase 4 study in adults and adolescent participants with asthma receiving medium-dose to high-dose ICS with additional controller(s) (eg, long-acting β2 Agonist [LABA], leukotriene receptor antagonist, theophylline, long-acting muscarinic antagonist [LAMA], cromones) in the prior 12 months with documented history of at least 2 asthma exacerbations in the prior year. Eligible participants are those for whom tezepelumab may be prescribed based on the assessment of their treating specialist physician, in accordance with the approved USPI, and those who have consented for the study.

The study will be divided into 2 periods:

- **Baseline Period (Week -52 to 0):** The baseline period is 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) is 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 (Week -4 to 0)**: The Informed Consent Form (ICF), or Assent Form, will be signed before any screening or study-specific activities are initiated. Eligibility criteria will be checked at Visit 1.
  - **Enrolment date**: Enrolment date may be on the same day of screening (Visit 1) or after, but before any mandatory study-specific procedures.
    - Participants will be asked to complete patient-reported outcome (PRO) questionnaires, lung function assessment, and clinical/laboratory tests at Visit 1 or before dosing at Visit 2 (see Section 9.4.2.2).
- **Study Period (Week 0 to 52)**
  - **Index date (Week 0)**: Date that participants receive the first tezepelumab dose at Visit 2.
    - To accommodate local healthcare practice, the index date (Visit 2) may be on the same day or after the enrolment date, provided the participants' eligibility has been confirmed. However, there should be no more than 4 weeks between screening (Visit 1) and index date (Visit 2).
  - **Treatment Period (Week 0 to 48)**: The treatment period with tezepelumab dose will be from Visit 2 (Week 0) until Visit 14 (Week 48). The **follow-up period (Week 48 to 52)** includes the post-dosing follow-up period (Weeks 48 to 52) and end of treatment (EOT) assessment at Visit 15 (Week 52).
    - Participants will visit the Investigator's site every 4 weeks for tezepelumab administration and routine care.
    - During Visit 8 (Week 24) and Visit 15 (Week 52), participants will be asked to complete PRO questionnaires, lung function assessment, and/or clinical and laboratory tests.
    - All serious adverse events (SAEs), adverse events leading to discontinuation of tezepelumab (DAEs), and Adverse event of Special Interest (AESIs) will be 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 will be 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.

Disclosure Statement: This is a single-arm study.

Masking: No masking of treatment.

Number of Participants:

Approximately 400 participants will enter the treatment period (consent/assent and dose) in a two-target approach in order to describe effectiveness in i) a broad population of patients across traditional asthma phenotypes of high and low blood eosinophils and allergic status (Phase 1) and ii) several under-studied populations of interest (Phase 2). The two-target categories are not distinctive or mutually exclusive as enrolment in Phase 1 will be regardless of characteristics relevant for Phase 2 (see Figure 2 in Section 4.1). Baseline blood eosinophil count (BEC) for Phase 1 and 2 classification will be based on the highest documented BEC during the 12-month baseline period or prior to the first tezepelumab dose at Visit 2, excluding counts within 0-30 days following systemic corticosteroid (SCS) use.

- Phase 1 will target approximately 50 participants in each of the following four subgroups (regardless of characteristics relevant for Phase 2):
  - Participants with a clinically-relevant allergy to a perennial aeroallergen and with a baseline BEC ≥ 300 cells/microliter.
  - Participants without a clinically-relevant allergy to a perennial aeroallergen and with a baseline BEC ≥ 300 cells/microliter.
  - Participants with a clinically-relevant allergy to a perennial aeroallergen and with a baseline BEC < 300 cells/microliter.
  - Participants without a clinically-relevant allergy to a perennial aeroallergen and with a baseline BEC < 300 cells/microliter.

  Note: In this study, clinically-relevant allergy to a perennial aeroallergen is defined as a clinical history of asthma symptoms driven by exposure to a perennial aeroallergen and sensitization to the corresponding aeroallergen(s) based on a positive result to serum allergen-specific immunoglobulin E (IgE) testing by Fluorescent Enzyme Immunoassay (FEIA) at baseline.
- Phase 2 will target increasing cumulative enrolment to approximately 50+ participants in each of the following four subgroups (balanced within each subgroup approximately equally between participants with a baseline BEC ≥300 and <300 cells/microliter):
  - Participants who identify as Black/African American
  - Adolescents (aged 12-17 years)
  - Comorbid diagnosis of mild to moderate COPD, consistent with GOLD guidelines (GOLD 2021)

- History of ≥10 pack-years of smoking (including current or previous smokers).

Note: Participants in these subgroups will not be mutually exclusive. Participants may be counted in all subgroups for which they qualify. All subgroups will be monitored during study recruitment and may be kept closed at the discretion of the study sponsor, even if target enrolment is not reached.

Intervention Groups and Study Duration

Single arm study.

- Total duration for the study for each participant could be up to 56 weeks:
  - Screening: up to 4 weeks.
  - Study Period: 52 weeks.
    - Treatment period: 48 weeks.
    - Follow-up period: 4 weeks.
- Participants will receive up to 13 subcutaneous injections of tezepelumab 210 mg with the first injection at Week 0 and the last injection at Week 48 (injection every 4 weeks).

Scientific Committee: A scientific steering committee has supported development of the study protocol and design. The Scientific Committee will continue to be involved in the study.

Statistical Methods

There is no predefined study hypothesis to test in this study; as such, no multiplicity control strategy will apply. This study is descriptive in nature; hence, all analyses will follow an estimation-based approach. The sample size of 400 participants is based on practical considerations and the ability to obtain a sufficient sample of participants across traditional asthma phenotypes and approximately 50+ participants in subgroups of interest: participants who identify as Black/African American, adolescents, those with comorbid diagnosis of mild to moderate COPD, and those with significant smoking history.

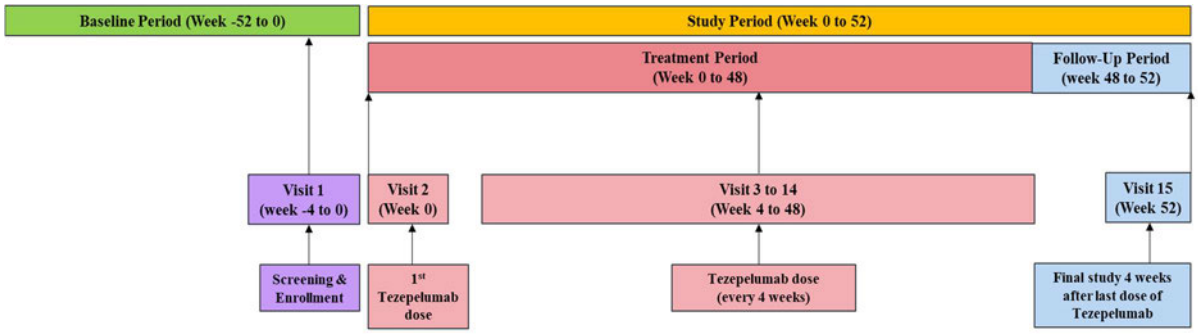
- The primary objective of this study is to describe and compare the rates of asthma exacerbations in the 12-month baseline period and the 12-month post-baseline period of treatment with tezepelumab. This will be achieved by performing an analysis of the incidence of exacerbations 12 months after the index date compared to the 12-month baseline period prior to the index date. The annual exacerbation rate is 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, will not be included in the calculation of time at risk for an exacerbation.

- Any asthma exacerbation that occurs within 7 days of the last dose of SCS, a temporary increase in stable oral corticosteroids (OCS) background dose, date of ED/UC visits or date of hospital discharge for a prior exacerbation will be counted as the same exacerbation event.

Other efficacy parameters and change from baseline in these parameters will also be summarized. Safety will be assessed by describing the number and proportion of participants with SAEs, DAEs, and AESIs.

1.2 Schema

Figure 1 Study Design



1.3 Schedule of Activities

Table 1 Schedule of Activities

	Baseline Period[a]	Study Period									Early Termination Visit[b]	Details in CSP Section or Appendix
	Screening	Treatment Period								Follow-up Period		
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9-14**	**V15**		
Week	**W-4 to W0**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28 to W48**	**W52**		
Visit Window (days)			**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Inclusion/exclusion criteria[a]	X											Section 5
Informed consent or assent	X											Section 5.1
Routine Clinical Procedures												
Key demographics (including race and ethnicity)	X											Section 4
Medical History[a]	X											Section 4
Prior and Concomitant medications	X	X	Data about concomitant medications will be collected throughout the study period								X	Section 6.5
Asthma history and treatment[a]	X									X	X	Section 4
Blood eosinophil count[c]	X	X								X	X	Section 8.8.2
Total IgE[d]	X	X								X	X	Section 8.4
Allergy testing (specific IgE)[d]	X	X								X	X	Section 8.4
Clinical safety laboratory assessments[d]	X	X										Section 8.5.3

	Baseline Period[a]	Study Period									Early Termination Visit[b]	Details in CSP Section or Appendix
	Screening	Treatment Period								Follow-up Period		
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9-14**	**V15**		
Week	**W-4 to W0**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28 to W48**	**W52**		
Visit Window (days)			**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Collection of results of other clinical tests of interest conducted as part of routine clinical practice (X-ray, CT scan, FeNO)[a]	X							X[f]		X[f]	X[f]	Section 8.5.4
Weight and height[e]	X	X								X		Section 8.5.2
Study Assessments												
Asthma exacerbations[a]	X	X						X[f]		X[f]	X[f]	Section 8.1.1
Asthma-related HRU[a]	X	X						X[f]		X[f]	X[f]	Section 8.3
Lung function test[g]	X	X						X		X	X	Section 8.1.3
Asthma medication use, including SCS[a]	X	X						X[f]		X[f]	X[f]	Section 8.1.2
ACQ-6[h]		X						X		X	X	Section 8.1.4.1
AIRQ[h]		X						X		X	X	Section 8.1.4.2
SGRQ[h,i]		X						X		X	X	Section 8.1.4.3
TSQM-9								X		X	X	Section 8.1.4.4
CGI-C								X		X	X	Section 8.1.4.5
TNSS[h]		X						X		X	X	Section 8.1.4.6
Asthma trigger survey[h]		X								X	X	Section 8.1.4.7
SNOT-22[j]		X						X		X	X	Section 8.1.4.8

	Baseline Period[a]	Study Period									Early Termination Visit[b]	Details in CSP Section or Appendix
	Screening	Treatment Period								Follow-up Period		
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9-14**	**V15**		
Week	**W-4 to W0**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28 to W48**	**W52**		
Visit Window (days)			**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
PGI-C[h,k]								X		X	X	Section 8.1.4.10
Participant experience interview[l]										X	X	Section 8.1.4.11
SAEs/DAEs/AESIs		Data about SAEs, DAEs, and AESIs will be collected throughout the study period										Section 8.6
Pregnancy test (for female participants only)	X	As clinically appropriate										Section 8.6.10
Study Treatment												
Administration of tezepelumab		X	X	X	X	X	X	X	X			Section 6.1 and 6.2

[a] All participants will have the following routine clinical procedures and study assessments collected during the 12-month baseline period prior to the index date (Visit 1 (and Visit 2 if performed separately)) and, for some parameters, during the 12-month post-baseline period: medical history (including historical laboratory data) and concomitant medications, asthma history, asthma exacerbation, asthma-related HRU, SCS use, and any other clinical tests of interest from the healthcare provider based on medical record review.

[b] Participants who prematurely discontinue treatment with tezepelumab should be encouraged to continue with their remaining follow-up visits and procedures until the end of follow-up (Visit 15). All participants who prematurely discontinue treatment with tezepelumab should return to the study site and complete the procedures described for the Early Termination Visit within 4 weeks (± 7 days) after their last tezepelumab administration. All participants who withdraw their consent to participate in the study should be encouraged to return to the study center one last time to complete the procedures described for the Early Termination Visit within 4 weeks (± 7 days) after last tezepelumab administration.

[c] Baseline BEC for Phase 1 and 2 classification will be based on the highest documented BEC during the 12-month baseline period ***or*** prior to the first tezepelumab dose at either Visit 1 or Visit 2, excluding counts within 0-30 days following SCS use.

[d] Participants will be asked to complete clinical safety laboratory assessments, total IgE testing and serum allergen-specific IgE testing by FEIA at either Visit 1 or before tezepelumab dosing at Visit 2.

[e] Weight to be measured at Visit 1 or 2 and Visit 15. Height to be measured at Visit 1 or 2 only.
[f] Data about asthma exacerbations, HRU, and results of any clinical tests of interest conducted as part of routine clinical practice will be collected from medical record extraction during study period.
[g] Participants will complete pre-bronchodilator and post-bronchodilator FEV1 (lung function assessment) at either Visit 1 or Visit 2, as well as Visit 8 and Visit 15. When the lung function assessment is performed at dosing visits (Visit 2, Visit 8, Visit 15), the pre-BD assessment will be performed pre-tezepelumab dose and the post-BD assessment will be performed post-tezepelumab dose. (Section 8.1.3).
[h] Participants will be asked to complete COA questionnaires before tezepelumab dosing at Visit 2.
[i] FPC, a composite endpoint in this study, will 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)…" (see Section 8.1.4.9).
[j] Assessment of SNOT-22 is only for participants with an ongoing diagnosis of chronic rhinosinusitis with or without nasal polyps (defined as an ongoing history of 'Rhinitis,' 'Chronic Sinusitis,' and/or 'Nasal Polyps' on the Respiratory Medical History eCRF) at baseline, regardless of whether symptoms are present on the day of Visit 1 or 2.
[k] PGI-C will only be administered to those with ongoing diagnosis of COPD prior to tezepelumab dosing at Visit 2.
[l] Qualitative Participant Interviews will not be conducted for all participants, but for up to 50 participants recruited across the 4 subgroups outlined in Phase 1 and Phase 2 (see Section 4.1).

Abbreviations: AESI = Adverse event of Special Interest; ACQ-6 = Asthma Control Questionnaire 6; AIRQ = Asthma Impairment and Risk Questionnaire; BD bronchodilator; BEC = blood eosinophil count; CGI-C = Clinical Global Impression of Change; COA = Clinical Outcome Assessment; COPD = chronic obstructive pulmonary disease; CSP = Clinical Study Protocol; DAE = adverse event leading to discontinuation of tezepelumab; FEIA = Fluorescent Enzyme Immunoassay; FeNO = Fractional Exhaled Nitric Oxide; FEV_1 = forced expiratory volume in 1 second; HRU = Healthcare resource utilization; IgE = immunoglobulin E; SAE = serious adverse event; SCS = Systemic corticosteroid; SGRQ = St. George's Respiratory Questionnaire; SNOT-22 = Sino-nasal Outcome Test; TNSS = Total Nasal Symptom Score; TSQM-9 = Treatment Satisfaction Questionnaire from Medication; V = visit; W = week.

2 INTRODUCTION

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 the 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.

As demonstrated in the PATHWAY (Phase 2b) and NAVIGATOR (Phase 3) studies, tezepelumab is the first and only biologic to consistently demonstrate exacerbation reduction in a broad population of severe asthma subjects across phenotypes and irrespective of biomarker levels, with a 71% and 56% annualized asthma exacerbation rate (AAER) reduction in the overall study populations in PATHWAY and NAVIGATOR (Corren et al., 2017; Menzies-Gow et al., 2021a).

Tezepelumab (TEZSPIRE™) has been approved in the US for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma (Appendix H, TEZSPIRE USPI 2021).

2.1 Study Rationale

Asthma is a syndrome characterized by airway inflammation, reversible airway obstruction, and airway hyperresponsiveness. Patients present clinically with recurrent wheezing, shortness of breath, cough, and chest tightness. Asthma is a leading cause of morbidity with a global prevalence of approximately 358 million (GINA 2021). The prevalence of severe asthma as a percentage of all asthma varies from country to country, largely due to variation between clinical and epidemiological definitions (Wenzel 2003) and is estimated to be 5% to 10% of the total asthma population (Barnes and Woolcock 1998; O'Byrne et al., 2012; Chung et al., 2014; Busse et al., 2000). Despite treatment with standard of care medications, including currently available biologic therapies, many severe asthma patients have uncontrolled disease, which is associated with a high risk of exacerbations, hospitalizations, and high healthcare costs (Corren et al., 2017; Menzies-Gow et al., 2020a).

TSLP, an epithelial cytokine, occupies an upstream position in the asthma inflammatory cascade and plays a central role in the initiation and persistence of airway inflammation in asthma. TSLP regulates immunity at the airway barrier surface, affecting dendritic cells and other innate and adaptive immune cells, and inducing downstream inflammatory processes

and bronchial hyper-responsiveness (Gauvreau et al., 2020). TSLP has also been shown to have effects on airway structural cells (eg, fibroblasts and airway smooth muscle) (Gauvreau et al., 2020). In asthma, both allergic and non-allergic triggers induce TSLP production. Tezepelumab is an anti-TSLP, human monoclonal antibody (mAb) (IgG 2λ) that binds to human TSLP with high affinity and prevents its interaction with the heterodimeric TSLP receptor (Corren et al., 2017; Gauvreau et al., 2014). By blocking the interaction of TSLP with its receptor complex, tezepelumab reduces the initiation and persistence of airway inflammation in asthma by interfering with multiple downstream inflammatory pathways, as evidenced by the reduction from baseline in multiple biomarkers and cytokines (eg, eosinophils, IgE, FeNO, IL-5, and IL-13) in severe asthma participants treated with tezepelumab (Corren et al., 2017; Pham et al., 2019). Clinical efficacy and safety of tezepelumab was demonstrated in the PATHWAY Phase 2b trial and confirmed in the NAVIGATOR Phase 3 global safety and efficacy randomized clinical trial (RCT) among severe asthma participants treated with tezepelumab added to standard of care (medium- or high-dose inhaled corticosteroids plus at least one additional controller medication with or without oral corticosteroids) (Corren et al., 2017; Menzies-Gow et al., 2021a).

Post-approval effectiveness studies are important to complement and establish the generalizability of RCT results. Benefits of post-approval effectiveness studies include assessing effectiveness in a broader, more representative patient population than that enrolled in the Phase 3 RCTs, evaluating effectiveness in different subpopulations and participants with relevant comorbidities, and providing data describing real-world patient characteristics, adherence/persistence, and drug safety (Ramagopalan et al., 2020; Suvarna 2018).

The purpose of PASSAGE is to assess the effectiveness of tezepelumab in the US among a broader and more representative population than Phase 3 RCTs. The study population will consist 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 will include 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, and 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 (Ambrose et al., 2020; Moore et al., 2020).

2.2 Background

Several biologic therapies have been shown to reduce AAER in severe asthma patients who are uncontrolled with medium- to high-dose ICS and additional asthma controller medications. Omalizumab provided benefit for a subgroup of patients with proven reactivity to a perennial aeroallergen and who were inadequately controlled with ICS (XOLAIR USPI 2021). Four additional biologics, mepolizumab, reslizumab, benralizumab, and dupilumab, have recently been approved for severe asthma with an eosinophilic phenotype (NUCALA USPI 2021; CINQAIR USPI 2020; FASENRA USPI 2019; DUPIXENT USPI 2021). Biologics targeting IgE, IL-5/5R, and IL-4R are now included in international treatment guidelines (GINA 2021) as add-on treatment for patients uncontrolled with ICS/LABA treatment. However, patients without an allergic or eosinophilic phenotype (not OCS dependent) are ineligible for these agents. Additionally, among those receiving currently available biologics, substantial proportions of patients continue to experience exacerbations and may benefit from agents that target different molecular pathways (Wenzel 2016; Froidure et al., 2016; Swedin et al., 2017). Therefore, there is a clear unmet medical need for additional treatments among patients with severe asthma, independent of allergic or eosinophilic status.

Clinical efficacy and safety of tezepelumab was demonstrated in the PATHWAY Phase 2b trial and confirmed in the NAVIGATOR Phase 3 global safety and efficacy randomized clinical trial among severe asthma participants treated with tezepelumab added to standard of care (medium- or high-dose ICSs plus at least one additional controller medication with or without oral corticosteroids). As demonstrated in the PATHWAY and NAVIGATOR studies, tezepelumab is the first and only biologic to demonstrate consistent exacerbation reduction in a broad population of severe asthma subjects across phenotypes and irrespective of biomarker levels, with 71% and 56% AAER reduction in the overall study population in PATHWAY and NAVIGATOR (Corren et al., 2017; Menzies-Gow et al., 2021a). In these studies, tezepelumab 210 mg every 4 weeks (Q4W) was well tolerated in subjects with severe, uncontrolled asthma. The safety profile of tezepelumab is summarized in the United States Prescribing Information (USPI) (Appendix H, TEZSPIRE USPI 2021).

2.3 Benefit/Risk Assessment

The benefit/risk of tezepelumab is supported by the US FDA approval, as described in the USPI (Appendix H, TEZSPIRE USPI 2021).

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

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** • Annualized asthma exacerbation rate (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)tezepelumab
	Population: Adults and adolescents with asthma requiring medium- to high-dose inhaled corticosteroids (ICS), requiring additional controller(s), and those with at least 2 asthma exacerbations in the prior year who received at least one dose of tezepelumab **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). **Summary measure**: Annual asthma exacerbation rate ratio and corresponding

Objectives	Estimand Description/Endpoints
	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, emergency department/urgent care (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-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV_1) • Change from baseline in pre-BD FEV_1 • Proportion of pre-BD FEV_1 responders (defined as participants who achieve either at least 5% or 100 mL improvement from baseline)
To describe Asthma Control Questionnaire (ACQ-6), Asthma Impairment and Risk Questionnaire (AIRQ), and St. George's Respiratory Questionnaire (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])

Objectives	Estimand Description/Endpoints
	• Proportion of SGRQ responders (defined as participants who achieve ≥1 MCID[b])
To describe systemic corticosteroid (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 healthcare resource utilization (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: • Blood eosinophil count (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 serious adverse events, adverse events that lead to tezepelumab treatment discontinuation, and adverse events of special interest

Objectives	Estimand Description/Endpoints
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 • Number of administered tezepelumab injections • 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-bronchodilator (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 Treatment Satisfaction Questionnaire from Medication (TSQM-9) and physician clinical global impression of change (CGI-C) in months 6 and 12 after initiation of tezepelumab	• TSQM-9 score • CGI-C score
To describe frequent productive cough (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 Global Impression of Change (PGI-C) score for COPD

Objectives	Estimand Description/Endpoints
To describe total nasal symptom score (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 ≥1 MCID[b])
To describe participant-reported causes of asthma symptoms or asthma attacks as reported within an asthma trigger survey at baseline and month 12, and asthma exacerbations and asthma-related HRU (sample permitting) during the 12-month periods before (baseline period) and after initiation of tezepelumab (study period) as a function of participant-reported trigger categories/number of reported triggers	• 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
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 Sino-nasal Outcome Test (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 will be defined by worsening of asthma symptoms that leads 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 must justify the decision for defining an event of worsening asthma as an exacerbation.

[b] Minimum clinically important difference (MCID) will be defined in the Statistical Analysis Plan (SAP).

[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 immunoglobulin E (IgE) testing by Fluorescent Enzyme Immunoassay (FEIA) at baseline.

[d] Consistent with GOLD 2021 guidelines.

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

[f] Exploratory subgroup of participants will be defined in the Statistical Analysis Plan (SAP).

4 STUDY DESIGN

4.1 Overall Design

- This is a multicenter, single-arm, open-label, post-authorization, Phase 4 study in adults and adolescent participants with asthma receiving medium-dose to high-dose ICS with additional controller(s) for at least 12 months prior to Visit 1 with documented history of at least 2 asthma exacerbations during the year prior to Visit 1.
- All participants are those deemed eligible and appropriate for tezepelumab based on the assessment of their treating specialist physician in accordance with the approved USPI and who have consented for the study.
- Tezepelumab will be provided at no cost to all participants during the entire study duration per protocol.
- The study aims to evaluate the effectiveness of tezepelumab over the duration of 52 weeks, after initiation of a 210 mg dose of subcutaneous (SC) tezepelumab Q4W.
- The total duration of the study for each participant will be approximately 56 weeks.

The study will be divided into 2 periods:

- **Baseline Period (Week -52 to 0):** The baseline period is 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) is 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 (Week -4 to 0)**: The Informed Consent Form (ICF), or Assent Form, will be signed before any screening or study-specific activities are initiated. Eligibility criteria will be checked at Visit 1.
  - **Enrolment date**: Enrolment date may be on the same day of the screening (Visit 1) or after, but before any mandatory study-specific procedures.
    - Participants will be asked to complete patient-reported outcome (PRO) questionnaires, lung function assessment, and clinical and laboratory tests at Visit 1 or before dosing at Visit 2 (see Section 9.4.2.2).
- **Study Period (Week 0 to 52)**
  - **Index date (Week 0)**: Date that participants receive the first tezepelumab dose at Visit 2.
    - To accommodate local healthcare practice, the index date (Visit 2) may be on the same day or after the enrolment date, provided the participants' eligibility has

been confirmed. However, there should be no more than 4 weeks between screening (Visit 1) and index date (Visit 2).

- **Treatment Period (Week 0 to 48)**: The treatment period with tezepelumab dose will be from Visit 2 (Week 0) until Visit 14 (Week 48). The **follow-up period** (Weeks 48 to 52) includes the post-dosing follow-up period (Weeks 48 to 52) and end of treatment (EOT) assessment at Visit 15 (Week 52).
  - Participants will visit the Investigator's site every 4 weeks for tezepelumab administration and routine care.
  - During Visit 8 (Week 24) and Visit 15 (Week 52), participants will be asked to complete PRO questionnaires, lung function assessment, and/or clinical and laboratory tests.
  - All serious adverse events (SAEs), adverse event leading to discontinuation of tezepelumab (DAEs), and adverse events of special interest (AESIs) will be recorded from the index date, throughout the tezepelumab treatment period (Weeks 0 to 48), and through the post-dosing follow-up period (Weeks 48 to 52).
  - Participants will be 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.

Approximately 400 participants will enter the treatment period (consent/assent and dose) in a two-target approach in order to describe effectiveness in i) a broad population of patients across traditional asthma phenotypes of high and low blood eosinophils and allergic status (Phase 1) and ii) several under-studied populations of interest (Phase 2). The two-target categories are not distinctive or mutually exclusive as enrolment in Phase 1 will be regardless of characteristics relevant for Phase 2 (see Figure 2). Baseline blood eosinophil count (BEC) for Phase 1 and 2 classification will be based on the highest documented BEC during the 12-month baseline period or prior to the first tezepelumab dose at Visit 2, excluding counts within 0-30 days following systemic corticosteroid (SCS) use.

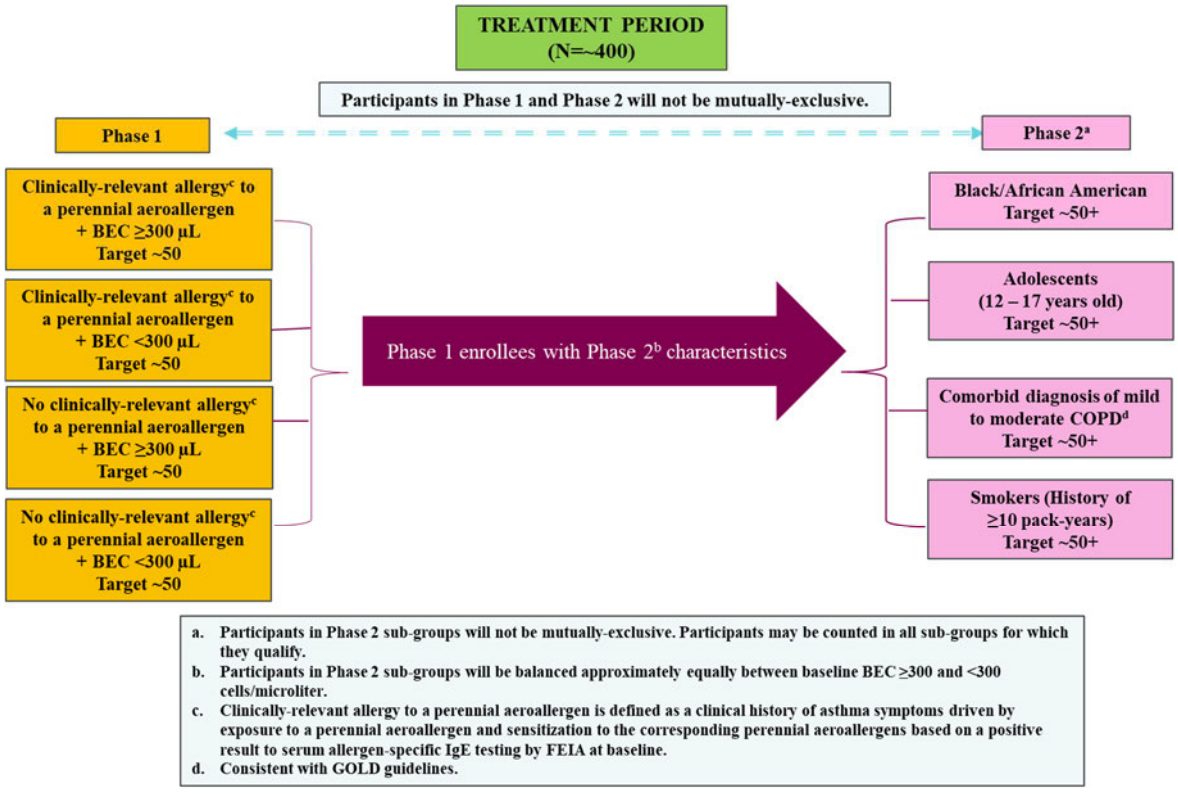
- Phase 1 will target approximately 50 participants in each of the following four subgroups (regardless of characteristics relevant for Phase 2):
  - Participants with a clinically-relevant allergy to a perennial aeroallergen and with a baseline BEC ≥300 cells/microliter.
  - Participants without a clinically-relevant allergy to a perennial aeroallergen and with a baseline BEC ≥300 cells/microliter.
  - Participants with a clinically-relevant allergy to a perennial aeroallergen and with a baseline BEC <300 cells/microliter.
  - Participants without a clinically-relevant allergy to a perennial aeroallergen and with a baseline BEC <300 cells/microliter.

Note: In this study, clinically-relevant allergy to a perennial aeroallergen is defined as a clinical history of asthma symptoms driven by exposure to a perennial aeroallergen and sensitization to the corresponding aeroallergen(s) based on a positive result to serum allergen-specific immunoglobulin E (IgE) testing by Fluorescent Enzyme Immunoassay (FEIA) at baseline.

- Phase 2 will target increasing cumulative enrolment to approximately 50+ participants in each of the following four subgroups groups (balanced within each subgroup approximately equally between participants with a baseline BEC ≥300 and <300 cells/microliter):
  - Participants who identify as Black/African American.
  - Adolescents (aged 12-17 years).
  - Comorbid diagnosis of mild to moderate COPD (consistent with GOLD guideline (GOLD 2021)).
  - History of ≥10 pack-years of smoking (including current or previous smokers).

  Note: Participants in these subgroups will not be mutually exclusive. Participants may be counted in all subgroups for which they qualify. All subgroups will be monitored during study recruitment and may be closed at the discretion of the study sponsor, even if target enrolment is not reached.

Figure 2 Treatment Period Phases 1 and 2 in the PASSAGE Study



Patients with comorbid chronic rhinosinusitis with nasal polyps are another population of interest and enrolment will be monitored to ensure sufficient recruitment of this population as well.

A Scientific Committee will be involved in the study (See Appendix A 5).

4.2 Scientific Rationale for Study Design

The purpose of PASSAGE, a multicenter, open-label, single-arm, post-authorization, Phase 4 study, is to assess the effectiveness of tezepelumab in the US among a broader and more representative population than Phase 3 RCTs. The study population will consist of adults and adolescent participants with asthma requiring medium-dose to high-dose ICSs with additional controller(s) (eg, LABA) in the prior 12 months, and with documented history of at least 2 asthma exacerbations in the prior year. The study population will include 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, and those with significant smoking history (≥10 pack-years of smoking).

While enrolling a broader, more real-world participant population than that enrolled in Phase 3 RCT, PASSAGE will also collect data on several endpoints that are not necessarily part of routine clinical practice. All participants are those deemed eligible and appropriate for tezepelumab based on the assessment of their treating specialist physician in accordance with the approved USPI and who have consented for the study.

The primary outcome (asthma exacerbations) and key secondary endpoints (including lung function and asthma control) are well-established outcome measures for a study in severe asthma (Doroudchi et al., 2020). These endpoints have been shown in the Phase 2b and Phase 3 studies to clearly differentiate the tezepelumab benefit from placebo.

4.2.1 Participant Input into Design

The study design concept was reviewed by patient representatives with severe asthma. Their request for a simple explanation of the study design and rationale will be incorporated into the ICF.

4.3 Justification for Dose

The selection of the 210 mg SC Q4W dose is as per the approved USPI.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of

the study including the last scheduled procedure shown in the Schedule of Activities (SoA).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Male or female participant must be 12 years of age or older, at the time of signing the ICF or assent.

Type of Participant and Disease Characteristics

2 Documented physician-diagnosed asthma for at least 12 months prior to Visit 1 and confirmed by the Investigator not to be due to alternative diagnoses.

3 Documented treatment with medium- to high-dose ICS as per GINA guidelines (GINA 2021) for at least 12 months prior to Visit 1 (see Appendix D).

4 Use of additional asthma maintenance controller medication(s) in addition to ICS (eg, LABA, leukotriene receptor inhibitors, theophylline, LAMA, and cromones) for at least 12 months prior to Visit 1. The additional maintenance controller medication may be contained in a combination product (eg, ICS/LABA).

5 Documented history of at least 2 asthma exacerbations during the 12 months prior to Visit 1. The definition of an asthma exacerbation in this study, and a list of acceptable documentation for historical exacerbations, are provided in Section 8.1.1.

6 Physician decision that participant is eligible for treatment with tezepelumab according to the approved USPI.

7 Currently receiving care from specialist physicians (eg, pulmonologists and/or allergists) at the Investigator's or sub-investigator's site.

Informed Consent

8 Provision of signed and dated written ICF prior to any mandatory study-specific procedures, sampling, and analyses for participants who are at, or over the age of majority (as per local law). For participants who are less than the age of majority, in addition to

their providing informed assent, the participants' legally authorized representative must also provide their informed consent. Participants must also be willing and able to comply with the requirements and restrictions listed in the ICF and in this protocol. The ICF process is described in Appendix A.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Any contraindication to tezepelumab as per the US approved product label or in the opinion of the Investigator.

2 Comorbid diagnosis of severe or very severe COPD per GOLD guidelines (GOLD 2021).

Prior/Concomitant Therapy

3 Use of biologics that are approved for the treatment of asthma within 4 months or 5 half-lives (whichever is longer) prior to Visit 1.

Prior/Concurrent Clinical Study Experience

4 Participation in an interventional clinical trial for asthma within 12 months prior to Visit 1.

Other Exclusions

5 Judgment by the Investigator that the participant is unlikely to comply with study procedures, restrictions, and requirements.

5.3 Lifestyle Considerations

No lifestyle restrictions will be required in this study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information that will be collected on the electronic Case Report Form (eCRF) includes demography, screen failure details, eligibility criteria, and any SAE.

5.4.1 Re-screening

Re-screening is allowed up to 2 times under the following circumstances:

- If the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits), participants may potentially be re-screened. These cases should be discussed with the sponsor-appointed study physician and documented in the investigator study file (ISF).
- Participants once their washout period is completed for exclusion criteria 3 or 4 (see Section 5.2).
- Participants once having at least 12 months of baseline period of relevant historical data through medical record review for the inclusion criteria (see Section 5.1).

Re-screening of a participant for any other reason will be allowed only upon approval of the sponsor-appointed study physician. A documented approval for re-screening should be filed in the ISF.

Re-screened participants should be assigned the same participant number as for the initial screening. It means that participant should keep the same E-code as was originally assigned.

Re-screening should be documented so that its effect on study results, if any, can be assessed. A participant who is re-screened is not required to sign another ICF if the re-screening occurs within 7 days from the previous ICF signature date. All assessments must be repeated for re-screening unless they are within 28 days of enrolment.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

The study intervention supplied to this study is representative of the commercially manufactured tezepelumab, and used in accordance with USPI.

6.1 Study Intervention Administered

Table 3 Investigational Product

Intervention name	Tezepelumab
Type	Biologic
Dosage form	Solution for injection
Unit Dose Strength(s)	210 mg

Dosage level(s)	210 mg Q4W
Route of administration	Subcutaneous injection
Use	Treatment of severe asthma per current approved USPI
Sourcing	Provided centrally by the sponsor or designee
Packaging and labelling	Study treatment will be provided either in 5 mL vials, or APFS. Each vial/APFS will be labelled in accordance with GMP Annex 13 and per country regulatory requirement
Former names(s) or alias(es)	AMG 157 or MEDI9929

Abbreviations: APFS = accessorized pre-filled syringes; GMP = Good Manufacturing Practice; Q4W = every 4 weeks; USPI = United States Prescribing Information.

Tezepelumab is a sterile, clear, colorless to slightly yellow solution. It will be supplied by AstraZeneca as a solution for injection in either a vial or accessorized pre-filled syringes (APFS) for administration in accordance with the approved USPI.

The study intervention vials/APFS's are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The study intervention must be kept in original packaging until use to prevent prolonged light exposure.

6.2 Preparation/Handling/Storage/Accountability

The study intervention will be supplied to the site in a kit with one vial or APFS of tezepelumab. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton).

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.2.1 Dose Preparation (Vials)

A dose of 210 mg will be administered as a single 1.9 mL injection using a needle size

suitable for SC injection (eg, 27G x 0.5). Each vial selected for dose preparation will be inspected. If there are any defects noted with the study intervention, the Investigator and site monitor should be notified immediately. Refer to the Product Complaint section for further instructions (Section 6.2.4).

The dose of tezepelumab must be prepared by the Investigator's or site's designated study intervention manager using aseptic technique. Vials should be equilibrated to room temperature for 30-60 minutes before dose preparation. Total time from needle puncture of the study intervention to start of administration must not exceed 4 hours at room temperature.

Tezepelumab vials do not contain preservatives; any unused portion of the vial must not be used for subsequent dosing.

To prepare the participant's dose, the study intervention will be selected for administration according to the kit identification numbers assigned by the interactive web/voice response system (IxRS). One vial of study intervention will be assigned by the IxRS for each dose.

The assigned vial should be used only once to prepare a single dose required at the dosing visit. Unused product in opened and dispensed vials should not be used for subsequent dosing and should be stored for study intervention accountability. If the opened and dispensed vials must be discarded immediately after dose preparation as per site's standard operating procedure (SOP), the kit boxes must be retained for study intervention accountability.

6.2.2 Dose Preparation (APFS)

Preparation of the study intervention must be performed by a qualified person (eg, pharmacist, Investigator, or nurse) at the site. The APFS should be visually inspected prior to dose preparation. If defects are noted with the study intervention, the Investigator and site monitor should be notified immediately.

The study intervention does not contain preservatives and any unused portion must be discarded. Total in-use storage time from removal of the study intervention from the refrigerator to start of administration must be within the allowable window documented in the USPI.

To prepare the participant's dose, a study intervention kit will be selected for administration according to the kit identification number assigned by the IxRS.

Dose preparation should be performed in accordance with the approved USPI.

Unused product in opened and dispensed study intervention kits must not be used for subsequent dosing and should be stored for study intervention accountability. If the opened and dispensed APFS must be discarded immediately after dose preparation as per the site's

SOPs, the kit boxes must be retained for study intervention accountability.

6.2.3 Dose Administration

The administration of tezepelumab should be recorded in the appropriate sections of the eCRF. The study intervention will be administered by one SC injection and by the Investigator/authorized delegate as specified in Table 1.

Each participant will receive tezepelumab 210 mg (one 1.9 mL injection), administered SC Q4W for 13 doses in the abdomen, thigh, or upper arm. The study physician/authorized delegate should follow the dosage and administration instruction in the approved USPI.

If any conditions require rescheduling of the visit for tezepelumab administration, the visit should be rescheduled within the allowed visit window and study intervention should be administered at that visit. If this is not possible the study intervention administration should be skipped. If a participant skips 2 consecutivestudy intervention administrations, the Investigator should contact the study physician to discuss the reason for the skipped doses.

6.2.4 Reporting Product Complaints

Preparation of study intervention must be performed by a qualified person (eg, pharmacist or Investigator) at the site. Any defects with the study intervention must be reported immediately to the site monitor. All defects will be communicated to the sponsor and investigated further with the AstraZeneca Supply Chain Group.

During the investigation of the product complaint, all study interventions must be stored at labelled conditions 2°C to 8°C (36°F to 46°F), separated from other study intervention kits, unless otherwise instructed.

6.2.5 Reporting Product Defects

Product defects may be related to component, product, or packaging and labelling issues prior to or during use. Product defects should be reported to the study monitor. The list below includes the 3 categories of product complaints that should be reported as defects. Descriptions of product complaints in these 3 categories include, but are not limited to:

- Component Issue: Defect in container or dosing mechanism of the study intervention. The component defect may be damaged, missing, or broken.
- Product Issue: Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that does not apply to the product description in Section 6.1.

- Packaging/Labelling Issue: Defect in the packaging or labelling of the product. The packaging (eg, carton, thermo-fitted tray, or tamper-evident seal) or labelling defects may be damaged or unreadable, or the label may be missing.

6.2.6 Single Use APFS Device Malfunction

An APFS malfunction is when the APFS appeared normal during verification of shipment and then does not work during administration, eg, the safety feature activated prematurely, part of the device (finger flange, plunger rod, etc.) came off or broke, needle shield could not be removed only partial dose administered, needle guard safety feature did not activate, or needle bent or broke upon use.

- Device malfunctions should be reported using the appropriate AstraZeneca Product Complaint Intake Form and the study monitor should be notified.
- If a device malfunction is identified at the study site:
  - Before study intervention administration has started, another study intervention kit (replacement) should be dispensed to perform study intervention administration.
  - After study intervention administration has started and participant has been administered unknown dose of study intervention, another study intervention kit must not be dispensed, and participant must not be administered with another study intervention kit. The contract research organization (CRO) study physician and study monitor should be notified.
- If it is determined that a replacement should be issued based on the same guidance for device malfunction at study site described above, the health care professional (HCP) will return to the study site to obtain the replacement device.
- Address and attention for malfunctioning device is available in the Device Malfunction Return Instructions.

For definitions and procedures for recording, evaluating, follow-up, and reporting of medical device AEs, SAEs and deficiencies in medical device studies, please see Section 8.6.13 and Appendix F.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is a single-arm study, as such, no randomization or blinding is required. However, the Investigator will assign each potential participant a unique enrolment number, beginning with ‘E#’ via an IxRS. IxRS will allow capping the number of participants in each study Phase, and within the subgroups in each study Phase (Section 4.1).

Before the study is initiated, access details to IxRS will be provided to each site. Specific information concerning the use of the IxRS will be provided in a separate manual.

If a participant withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn participants will not be replaced in the study.

The study intervention will be dispensed at the study visits summarized in SoA (see Table 1).

6.4 Study Intervention Compliance

Participants will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. If the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff. If the study intervention was missed or interrupted for any reason, the next dose of study intervention should be administered as soon as possible as per the USPI and the Investigator's judgment, avoiding more than one dose within a 2-week period (ie, overdose).

6.5 Prior and Concomitant Therapy

Information about all the concomitant treatments given during the study period (through follow-up period) with reason for the treatment will be collected by the Investigator/authorized delegate at each visit (as shown in Table 1) and recorded in the eCRF. Any changes to background medication will be made as required, per the study physician's discretion.

In order to satisfy inclusion criterion 3, receipt of medium-dose to high-dose ICS with additional controller(s) for the 12 months prior to enrolment date should be documented in source and recorded in the eCRF. Prior receipt of biologic treatments or maintenance SCSs for asthma will also be collected.

Asthma exacerbations should be treated with oral or other SCSs according to standard practice (see Section 6.5.1.1).

The study physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medicine

6.5.1.1 Management of Asthma Exacerbation During Treatment Period

Participants who experience an exacerbation during the treatment period should remain on tezepelumab at the Investigator's discretion. Asthma exacerbations should be treated according to standard clinical practice.

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

Participants who complete Visit 15 should be given standard of care, which may include commercially available tezepelumab, at the discretion of the Investigator. Tezepelumab will not be available via the study following the end of the Treatment Period (Visit 14).

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be appropriate for a participant to permanently discontinue (definitive discontinuation) tezepelumab. The decision to discontinue the study intervention will be based on the Investigator's assessment of the benefit and risk of continuing treatment with the study intervention, and after discussing this with the participant.

Reasons for discontinuation of the study intervention ***may*** include:

- Participant decision: The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- Incorrectly enrolled/dosed participant in whom the inclusion/exclusion criteria violation would put the participant at undue risk.
- Adverse event for which the Investigator judges continued treatment may put the participant at undue risk.
- Severe noncompliance with the CSP.
- Pregnancy (see Section 8.6.10).
- An anaphylactic reaction to the study intervention requiring administration of epinephrine.
- A helminth parasitic infestation not responding to anti-helminth treatment.

For discontinuation pertaining to COVID-19, please see Appendix C.

A participant who decides to discontinue tezepelumab will always be asked about the reason(s) and the presence of any AEs. The reason for premature discontinuation of tezepelumab should be documented in the source documentation and recorded in the eCRF.

All participants who prematurely discontinue study drug should return to the study site and complete the procedures described for the Early Termination Visit within 4 weeks (± 7 days)

after last tezepelumab administration. All participants who prematurely discontinue tezepelumab should be encouraged to return for all regularly scheduled visits for safety and efficacy assessments (see Table 1).

At the Early Termination Visit the participants will be given the following 2 options as to how they will be followed:

1. The participant should be encouraged to return for all regular clinic visits and perform all scheduled assessments (excluding study intervention administration) until the EOT visit at Week 52 (± 7 days).
2. The participant will be offered follow-up on a monthly basis via telephone calls, and will not participate in any other procedures until he/she completes the on-site EOT visit at Week 52 (± 7 days).

If a participant chooses option 1, all assessments will be completed as per the SoA as indicated in Table 1. If a participant chooses option 2, the key information to be collected during the telephone calls include SAEs, DAEs, AESIs, changes in concomitant medication, and asthma exacerbation information.

If a participant discontinues tezepelumab due to a study-specific discontinuation criterion, this should always be recorded as 'Development of study-specific discontinuation criteria' in the eCRF.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study. The EOT visit will be completed immediately in the case of subsequent early withdrawal from the study. Participants who do not wish to have any follow-up contacts will be discontinued from the study.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request (ie, participant withdrawal of consent for the study), or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Termination Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed. The participant will discontinue the study intervention and be withdrawn from the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the study team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

8.1.1 Assessment of Asthma Exacerbation

During the study, an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of SCSs (or a temporary increase in stable OCS background dose) for at least consecutive 3 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.
- An emergency room (ED)/ or urgent care (UC) visit (defined as evaluation and treatment for <24 hours in an ED/UC center) due to asthma that required SCSs (as per the above).
- An inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma.

Exacerbations should be recorded consistently during the 52 weeks before (baseline period) and after initiation of tezepelumab (study period) as per local practice, for example in form of:

- Discharge summaries from a hospital or ED/UC facility indicating that a participant was hospitalized/treated with systemic steroids for an asthma exacerbation.
- Evidence of prescriptions for systemic steroids used during an exacerbation.

- A documented conversation that is recorded in a timely manner between the study physician/nurse or nurse practitioner and a participant who is already on an OCS action plan, detailing the diagnosis and treatment of an asthma exacerbation.
- A documented conversation between the treating/referral physician or nurse/nurse practitioner certifying that a participant was treated for an exacerbation with steroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure participant records have been unsuccessful.

The Investigator must justify the decision for defining an event of worsening asthma as an exacerbation and record it in the source documents and eCRF.

The participant should remain in the study after an exacerbation and continue to receive tezepelumab if the Investigator judges that it is medically appropriate for the participant to do so and will be managed as per the details provided in Section 6.5.1.1.

Changes in concomitant medications due to exacerbations must be recorded in the appropriate module of the eCRF.

Asthma exacerbations will be collected at Visit 1 (and Visit 2 if performed seperately) for the baseline period and data collected at the 6-month interval (Visit 8 and Visit 15) from medical record extraction during the study period in accordance with the SoA (Table 1).

8.1.2 Assessment of SCS Use

Assessment of SCS use will be collected throughout at Visit 1 (and Visit 2 if performed seperately) for the baseline period and data collected at 6-month interval (Visit 8 and Visit 15) during the study period from the healthcare provider based on medical record review in a uniform manner for every participant using an eCRF in accordance with the SoA (Table 1). These will include:

- Any SCS at any timepoint before and after index date,
- Cumulative annualized SCS dose (in prednisone equivalent dose) in the time period before and after index date,
- Participants requiring long-term SCS use (>30 consecutive days).

SCS use for asthma will be separated out for maintenance OCS and OCS bursts associated with asthma exacerbations. All SCS use for asthma will be documented in the source documentation and recorded in the appropriate eCRF form.

8.1.3 Spirometry

General requirements

Lung function (FEV_1) will be measured pre-BD and post-BD at the study site by spirometry using local spirometry equipment.

Spirometry will be performed by the Investigator, or designee, according to the American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines that are being used at the study sites.

Spirometry calibration and data quality checks (including monitoring of unexpectedly high variability of results) will be detailed in a separate spirometry procedures manual and in the monitoring plan.

- Participants should avoid engaging in strenuous exertion for at least 60 minutes prior to all lung function assessments at the study site.
- Participants should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the study site.
- Participants should withhold their usual background therapies on the day(s) when lung function testing is being performed as below:
  - Short-acting β agonists and short-acting muscarinic antagonist should be withheld at least 6 hours prior to scheduled spirometry at the study site.
  - Twice daily LABA or LAMA containing therapies should be withheld for at least 12 hours prior to scheduled spirometry at the study site.
  - Once daily LABA or LAMA containing therapies should be withheld for at least 24 hours prior to scheduled spirometry at the study site.
  - Twice daily theophylline should be withheld for at least 12 hours prior to scheduled spirometry at the study site.
  - Once daily theophylline for at least 24 hours prior to scheduled spirometry at the study site.

Time of day for scheduled site visit spirometry

Spirometry testing should be done according to the SoA (Table 1) at either Visit 1 or Visit 2, as well as Visit 8 and Visit 15. It is recommended that all study period spirometry assessments are performed within ± 2 hours of the time of day that the Visit 1 spirometry is performed, if possible.

Spirometry technique

Forced expiratory maneuvers should be performed with the participant seated in an upright

position. If this is not comfortable for the participant, standing is permitted. The same position should be used by the participant for each forced expiratory maneuver from enrolment throughout the study. The head must not be tilted during maneuvers and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the maneuver. The participant should use mouthpieces of the same dimension and shape from enrolment throughout the study.

The FEV_1 should start with a maximal inspiration followed by a fast and forceful expiration that should last for at least 6 seconds. It is important to encourage the participant to continue the expiration to be fast and forceful throughout the maneuver. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak, or obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3, but no more than 8) will be performed for each site spirometry session. Spirometry grading will conform to ATS/ERS acceptability and reproducibility criteria as detailed in the spirometry manual. The highest FEV_1 and forced vital capacity (FVC) will be based on the best efforts meeting acceptability criteria. The highest recorded FEV_1 and FVC do not need to be from the same effort and can be derived from separate efforts. The absolute measurement (for FEV_1 and FVC) and the percentage of predicted normal (PN) value (Quanjer et al., 2012) will be recorded. Further details on spirometry are provided in the spirometry manual.

If the participant cannot tolerate a spirometry assessment during the visit, or if the participants' background medication has not been withheld as mentioned above, the spirometry assessment can be rescheduled for a different date, preferably within the visit window. There is no need to withhold study intervention in this case; it can be administered during the visit as scheduled.

Pre-BD and post-BD spirometry procedures will be obtained at all spirometry assessments specified in the SoA (Table 1):

- Pre-BD spirometry procedures will be completed before the participant's usual morning background respiratory therapy (if applicable) is administered, for the reasons discussed above. The tezepelumab dose should be administered after pre-BD spirometry is complete.
- Post-BD spirometry procedures will be completed following tezepelumab administration and approximately 15 to 30 minutes after the participant has taken bronchodilator (eg, 4 puffs of albuterol/salbutamol metered-dose inhaler).

Record keeping

A signed and dated copy of the spirometry printout must be kept at the study site for source

data verification. The printout must be marked with the study code, enrolment code, date, and time of measurement, and visit number. Date and time (and result) of the spirometry data will be transcribed from source data into the electronic database (in the Electronic Data Capture [EDC] system).

Spirometry references

The Global Lung Function Initiative equations will be used to determine the participants' PN values and are pre-programmed into the spirometer (Quanjer et al., 2012).

8.1.4 Clinical Outcome Assessments (COAs)

Clinical Outcome Assessment (COA) data will be captured electronically using a tablet device at the study site. The electronic PRO device will be the only acceptable source of COA data. Site personnel will be trained on using the tablet. Detailed procedures for using the device and training the participants will be described in a separate instruction manual. Participants will also be asked to verify completion of training on the tablet. Data for all PROs will be collected in accordance with Table 1. Participants should be informed that the recording must be completed within a defined time window. Participants will also be provided with information about when and where to request help if problems occur. The Investigator/authorized delegate will check the participant's adherence to completing the PRO assessment as described in Table 1.

Paper printouts of questionnaires and patient responses on paper questionnaires are not allowed; all data from paper questionnaires will be discarded and not part of the database.

8.1.4.1 Asthma Control Questionnaire 6 (ACQ-6)

The ACQ-6 (Juniper et al, 2006) is a shortened version of the ACQ that assesses the adequacy of asthma control and change in asthma control which occurs spontaneously or as a result of treatment. ACQ assesses symptoms and rescue bronchodilator use.

Participants have a 1-week recall (for items on symptoms and rescue inhaler use).

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤0.75 indicate well-controlled asthma, scores between 0.75 and ≤ 1.5 indicate partly controlled asthma, and scores >1.5 indicate not well-controlled asthma. Individual changes of ≥0.5 are considered to be clinically meaningful (minimum clinically important difference [MCID]). ACQ-6 responders in this study will be defined as participants who achieve ≥ 1 MCID.

The ACQ-6 will be completed at the site visits in accordance with the SoA during Visit 2 (prior to study intervention administration), Visit 8, and Visit 15 (Table 1).

8.1.4.2 Asthma Impairment and Risk Questionnaire (AIRQ™)

The AIRQ is a PRO tool intended to identify participants 12 years and older whose health may be at risk because of uncontrolled asthma. It has 10 questions that ask about respiratory symptoms, activity limitation, sleep, rescue medication use, social activities, exercise, difficulty controlling asthma, and exacerbations. All items have a yes/no response option, and the tool is scored by summing the total number of 'yes' responses. This sum score is used to assess level of asthma control where: 0-1 is well controlled, 2-4 is not well controlled, and 5-10 is very poorly controlled. Thus, a higher score indicates worse control status (Murphy et al., 2020).

The AIRQ items have 2 different recall periods: the first seven impairment items are evaluated over the past 2 weeks and the last three risk items either over the past 3 months or the past year. This study will use the version with a recall period for last three risk items over the past year at baseline/at the Week 52 EOT visits and the version with last three risk items for the past 3 months recall for the remaining visits where it is collected. AIRQ responders in this study will be defined as participants who achieve ≥ 1 MCID. The MCID for the AIRQ will be defined in the Statistical Analysis Plan (SAP).

The AIRQ will be completed at the site visits in accordance with the SoA during Visit 2 (prior to study intervention administration), Visit 8, and Visit 15 (Table 1).

8.1.4.3 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases (Jones et al., 1991). The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 components 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. SGRQ responders will be defined as participants who achieve ≥1 MCID. The MCID for SGRQ will be based on empirical data and interviews with patients, and will be defined in the SAP. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al., 2009).

The SGRQ will be completed at the site visits in accordance with the SoA during Visit 2 (prior to study intervention administration), Visit 8, and Visit 15 (Table 1).

8.1.4.4 Treatment Satisfaction Questionnaire from Medication (TSQM-9)

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

The TSQM-9 will be completed at the site visits in accordance with the SoA during Visit 8 and Visit 15 (Table 1).

8.1.4.5 Clinical Global Impression of Change (CGI-C)

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

The Investigator (clinician) will complete the CGI-C at the study site according to the SoA during Visit 8 and Visit 15 (Table 1). It is recommended that the same clinician completes the CGI-C at all applicable visits for an individual patient. Before making the assessment, the clinician will need to access and review the results from all relevant assessments including lung function measurements (FEV_1 and peak expiratory flow [PEF]) and PROs (ACQ-6 and AIRQ™) performed before the visit, adherence to the PROs should be closely monitored.

The CGI-C will be completed at the site visits in accordance with the SoA during Visit 8 and Visit 15 (Table 1).

8.1.4.6 Total Nasal Symptom Score (TNSS)

The TNSS is a brief questionnaire which evaluates the severity of main symptoms of allergic rhinitis that will be administered to all participants. It is defined as a total score composed of at least 3 of the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing. Each question can be answered using a 4-point scale from “0” (no symptoms) up to “3” (severe symptoms) (Downie et al., 2004). TNSS responders in this study will be defined as participants who achieve ≥ 1 MCID. The MCID for TNSS will be defined in the SAP.

The TNSS will be completed at the site visits in accordance with the SoA during Visit 2 (prior to study intervention administration), Visit 8, and Visit 15 (Table 1).

8.1.4.7 Asthma trigger survey

The asthma trigger survey is a one question survey administered to collect data on the activities and/or other factors that trigger asthma symptoms and/or attacks. The information

collected through the survey will provide participant-generated insights on what factors triggers symptoms or exacerbations. The asthma trigger survey will be completed at the site visits in accordance with the SoA during Visit 2 (prior to study intervention administration) and Visit 15 (Table 1).

8.1.4.8 SNOT-22

The Sino-nasal Outcome Test (SNOT-22) is a 22-item health-related outcomes assessment for sino-nasal conditions (Hopkins et al., 2009). The tool is a modification of the SNOT-20 (Piccirillo et al., 2002) where items related to nasal blockage and loss of sense of tastes and smell have been added and the importance rating has been removed. The 22-question SNOT-22 is scored as 0 (no problem) to 5 (problem as bad as it can be) with a total range from 0 to 110 (higher scores indicate poorer outcomes) (Hopkins et al., 2009). SNOT-22 responders will be defined as participants who achieve ≥ 1 MCID. The MCID for SNOT-22 will be defined in the SAP.

The SNOT-22 will be completed only for participants having an ongoing diagnosis of chronic rhinosinusitis with or without nasal polyps (defined as an ongoing history of 'Rhinitis,' 'Chronic Sinusitis,' and/or 'Nasal Polyps' on the Respiratory Medical History eCRF) at baseline, regardless of whether symptoms are present on the day of Visit 1 or 2. It will be completed at the site visits in accordance with the SoA during Visit 2 (prior to study intervention administration), Visit 8, and Visit 15 (Table 1).

8.1.4.9 Frequent productive cough (FPC)

Frequent productive cough (FPC) is a clinical trait common across the spectrum of obstructive lung disease such as asthma and COPD. 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)…". Responses to these items range from 0 to 4 ("Not at all" – 0, "Only with chest infections" – 1, "A few days a month" – 2, "Several days a week" – 3, and "Most days a week" – 4).

Participants will be classified as having FPC if they answered, "most days a week" or "several days a week," ie, scored ≥3 for each item. Participants who score ≤2 for either SGRQ item are classified as not having FPC.

8.1.4.10 Patient's Global Impression of Change (PGI-C)

The PGI-C scale is used to measure change in clinical status. In this study only participants with an ongoing diagnosis of COPD prior to tezepelumab dosing at Visit 2 will be asked to complete this scale to determine if there has been an improvement or decline in their disease.

The PGI-C will be completed at the site visits in accordance with the SoA during Visit 8 and Visit 15 (Table 1).

8.1.4.11 Qualitative Participant Experience Interview

Participant experience interviews will be conducted with up to 50 participants recruited across the two phases outlined in Figure 2. Participants will be purposefully sampled using a prespecified sampling frame to ensure representation across the four subgroups and demographic requirements.

Participants will be selected in a systematic approach to avoid any selection bias.

Qualitative experience interviews will be conducted via an online platform (eg, Zoom) using audio only at the end of the study period (Visit 15), or at an Early Termination Visit for participants who may not participate in the study until follow-up. Interviews will be semi-structured and non-interventional and conducted with English speaking asthma participants in PASSAGE. All interviews will be facilitated by a trained interviewer.

The purpose of these interviews is to capture qualitatively the participants' experiences of the treatment on their asthma symptoms. Interviews will be guided by a topic guide, to include open-ended questions focusing on asthma symptoms, impact of symptoms on health-related quality of life, and how these impacts may or may not change with study treatment. Study participants will consent for participation to be interviewed during study enrolment.

Recruitment will continue until data saturation is reached.

8.2 Asthma Clinical Remission

The criteria for asthma clinical remission on treatment will be evaluated based on ACQ-6, lung function, OCS status, and asthma exacerbation (Menzies-Gow et al., 2020b, Menzies-Gow et al., 2021b, Lommatzsch et al., 2022). Detailed criteria definition of asthma clinical remission will be provided in the SAP.

8.3 Healthcare Resource Utilization (HRU)

The HRU will be collected in the eCRF by the Investigator and studysite personnel for all participants throughout the study at Visit 1 (and Visit 2 if performed separately) for the baseline period and data collected at 6-month interval (Visit 8 and Visit 15) during the study period in accordance with the SoA (Table 1). Protocol-mandated procedures, tests, and encounters are excluded.

The data collected will be used to conduct the secondary analyses and will include:

- Number and type of asthma-related HRU per participant (inpatient and outpatient)
- Duration of hospitalizations (total days or length of stay, including duration by wards [eg, intensive care unit]).

8.4 Total IgE and Specific IgE

All participants will undergo serum allergen-specific IgE testing at baseline period (Visit 1 or prior to tezepelumab dosing at Visit 2) to ascertain if they have any clinically-relevant allergy to perennial or seasonal aeroallergens. In this study, clinically-relevant allergy to a perennial aeroallergen is defined as a clinical history of asthma symptoms driven by exposure to a perennial aeroallergen and sensitization to the corresponding aeroallergen(s) based on a positive result to serum allergen-specific IgE testing by FEIA at baseline.

Blood samples for total IgE will also be collected at timepoints specified in the SoA (Table 1).

8.5 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

8.5.1 Physical Examinations

Not applicable.

8.5.2 Vital Signs

Weight and height will be measured at timepoints specified in the SoA (Table 1). Weight and height measurements will be performed in light clothing and with shoes off. Body mass index will be calculated, but not captured in the eCRF.

8.5.3 Clinical Safety Laboratory Assessments

Laboratory safety assessments (listed in Table 4) will be performed locally at Screening.

Laboratory results should be reviewed by the Investigator/authorized delegate and evaluated for abnormalities that in the opinion of the Investigator would preclude study participation. The copy of the laboratory results report should be signed and dated by the Investigator/authorized delegate and retained at the study site.

The following laboratory variables will be measured.

Table 4 Laboratory Safety Variables

Hematology/Haemostasias (whole blood)	Clinical Chemistry (serum)
Hemoglobin (Hb)	Sodium (Na^+)
Red blood cell count	Potassium (K^+)
Absolute leukocyte count (white blood cell count) and differential	Low-density lipoprotein
Platelet count	Gamma glutamyl transferase
Hematocrit (Hct)	Glucose
Glycated hemoglobin (HbA1c)	Creatinine

Hematology/Haemostasias (whole blood)	Clinical Chemistry (serum)
	Alkaline phosphatase
	Alanine amino transferase
	Aspartate amino transferase
	Bilirubin, total

8.5.4 Other Clinical Tests of Interests

X-ray, computed tomography (CT) scan, and/or Fractional Exhaled Nitric Oxide (FeNO) will be collected if performed at the site as a part of routine care. These assessments will not be performed solely for the purpose of the study. Information will be collected retrospectively at 12 months prior to Visit 2 and for 6 months prior to Visit 8 and at Visit 15.

8.6 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE to be collected in this study.

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

- SAEs (as defined in Appendix B 2)
- DAEs
- AESIs (see Section 8.6.6).

8.6.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs, DAEs, and AESIs will be recorded from the time of signature of informed consent, throughout the tezepelumab treatment period, and through the post-dosing follow-up period (4 weeks after the last dose of tezepelumab).

If the Investigator becomes aware of a SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to the sponsor.

8.6.2 Follow-up of AEs and SAEs

Any SAEs, DAEs, AESIs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing SAEs/DAEs/AESIs at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each SAE, DAE, and AESI:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the study intervention (yes or no)
- Action taken with regard to study intervention
- AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.6.3 Causality Collection

The Investigator should assess causal relationship between study intervention and each SAE/DAE/AESI and/or Incident, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study

intervention?'.

For SAEs and Serious Incidents, causal relationship should also be assessed for other medication and study procedures and/or medical devices. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.6.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF, if they meet the definition of an SAE (as defined in Appendix B 2), DAE, or AESI (see Section 8.6.6). When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.6.5 Adverse Events Based on Examinations and Tests

Deterioration as compared to baseline period in laboratory values, vital signs or physical examinations performed as part of usual clinical care should only be reported as AEs if they fulfil the criteria for an SAE, DAE, or AESI.

If deterioration in a laboratory value, vital signs, or physical examinations is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE (only if it fulfils any of the SAE, DAE, or AESI criteria) and the associated laboratory result/vital sign/physical finding will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value).

8.6.6 Adverse Events of Special Interest

An AESI is an event of scientific and medical interest towards improving the understanding of tezepelumab. An AESI may be serious or non-serious, depending on how the AESI is defined below. An AESI that is serious (i.e., meets one of the seriousness outcomes [Appendix B 2]) will be reported as both an AESI and an SAE for the purposes of follow-up responsibility and safety reporting.

AESIs require close monitoring and reporting. For the purposes of this study, AESIs for tezepelumab are as follows:

- Serious cardiac events

- Serious hypersensitivity reactions (see Appendix E)
- Serious infections
- Helminth infections (serious or non-serious)
- All malignancies (Note: All malignancies will be considered 'serious' and reported as SAEs accordingly)
- Guillain Barre Syndrome (serious or non-serious)

8.6.7 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one (1) calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The reference document for definition of expectedness/listedness is the current approved tezepelumab USPI.

8.6.8 Disease Under Study

Asthma exacerbations (see Section 8.1.1) occurring during the treatment period should be recorded as an outcome measure in the eCRF. An asthma exacerbation should also be recorded as an AE if it fulfils any of the above criteria for an SAE, DAE, or AESI.

Symptoms of disease under study are those which might be expected to occur as a direct result of asthma (eg, wheeze, cough, chest tightness, dyspnea, breathlessness, and phlegm). These symptoms will only be recorded as AEs if they fulfil any of the above criteria for an SAE, DAE, or AESI.

8.6.9 Reporting of SAEs/DAEs/AESIs in Relation to COVID-19

For participants experiencing signs and symptoms indicating an infection that may be COVID-related, an attempt will be made to determine whether the COVID-19 virus is the infectious organism and the SAEs/DAEs/AESIs will be recorded accordingly. If a participant presents with clinical signs and symptoms suggestive of COVID-19, a test will be requested where possible:

- If the test is positive, record "COVID-19 positive" in the SAE/DAE/AESI field.
- If the test is negative, record "COVID-19 negative" in the SAE/DAE/AESI field, along with the SAE/DAE/AESI signs and symptoms and/or other diagnosis.

If a test has not been performed or result is not available and signs and symptoms, as judged by the Investigator, are suggestive of COVID-19 infection, record "COVID-19 suspected" in the SAE/DAE/AESI field. If the Investigator has other concurrent diagnoses for the participant's signs and symptoms (eg, pneumonia), these will be recorded as separate SAEs/DAEs/AESIs.

All SAEs/DAEs/AESIs should be reported in line with instructions for safety reporting documented in the CSP.

8.6.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention.

8.6.10.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

The eCRF will be used to report the pregnancy and the outcome of the pregnancy.

If any pregnancy occurs, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The Investigator should discuss with the participant the benefits and risks of continuing tezepelumab during pregnancy, as per the approved USPI. Treatment with the tezepelumab may be continued during the pregnancy only if the benefits of the treatment outweigh the risks, and if the participant agrees to continue treatment.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within **1 or 5 calendar days** for SAEs (see Section 8.6) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

8.6.10.2 Paternal Exposure

Pregnancy of the participant's partners will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented in the Pregnancy Report Form for conceptions occurring from the date of the first administration of study intervention until 16 weeks (5 half-lives) after the last administration of study intervention. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.6.11 Medication Error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Medication errors should be documented in the Medication Error Report.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.6.7) and **within 30 days** for all other medication errors.

The definition of a medication error can be found in Appendix B 4.

8.6.12 Management of Study Intervention-related Toxicities

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as

well as medical equipment to treat acute anaphylactic reactions, must be immediately available when study intervention is being administered. Study site personnel must be trained to recognize and treat anaphylaxis (Lieberman et al., 2010). Details on anaphylaxis management are provided in Appendix E.

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Sampson et al., 2006). Anaphylaxis typically manifest as 1 of 3 clinical scenarios:

- The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both and at least one of the following: a) respiratory compromise; or b) reduced BP or symptoms of end-organ dysfunction
- Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced BP or associated symptoms and/or persistent gastrointestinal symptoms
- Reduced BP after exposure.

After study intervention administration at all visits, participants should be observed per local standard of care for the appearance of any acute drug reactions.

8.6.13 Medical Device Deficiencies

Accessorized pre-filled syringes (APFS) are being utilized to deliver the study intervention under study. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of medical device deficiency that occur during the study with such medical devices.

The definition of a medical device deficiency can be found in Appendix F.

NOTE: Incidents and deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix F of the protocol.

The AstraZeneca Product Complaint Intake Form will be used to collect the deficiency. For third-party medical devices, the deficiency will be reported to the manufacturer, who will be responsible for fulfilling their regulatory obligations.

8.6.13.1 Time Period for Detecting Medical Device Deficiencies

- Medical device incidents or malfunctions of the medical device will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any medical device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiency is provided in Appendix F.

8.6.13.2 Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.6.13.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

- Medical device deficiencies that is associated with an SAE will be reported to the Sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The AstraZeneca Product Complaint Intake Form will be sent to Sponsor by email as follows:
  - Reporting a medical device deficiency to Clinical Supply Chain
    - For all medical device deficiencies, the Product Complaint Intake Form will be sent to the Clinical Supply Chain Representative at the mailbox GCSCProductComplaintOriginators@astrazeneca.com
  - Reporting a medical device deficiency with an associated SAE to Participant Safety
    - Where the medical device deficiency has caused an SAE, the Sponsor Study Representative works with the Study Site Investigator to complete the Clinical Study Medical Device/Device Constituent Report Form.
    - The Sponsor Study Representative then forwards the Clinical Study Medical Device/Device Constituent Report Form to the Patient Safety Data Entry Site at the mailbox AEMailboxClinicalTrialTCS@astrazeneca.com within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.
- Where an SAE has occurred in addition to the malfunction, the SAE will be recorded in the eCRF as detailed in Section 8.6.7.
- AstraZeneca will be the contact for receipt of medical device deficiency reports.

8.6.13.4 Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all medical device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of medical device deficiencies to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
- For further guidance on the definition of an SAE, see Appendix F of the CSP.

8.7 Overdose

A dose in excess of 280 mg administered within a 2-week period is considered an overdose.

There is currently no specific treatment in the event of overdose of study intervention and possible symptoms of an overdose are not established.

An overdose with associated SAEs, DAEs, or AESIs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the case report form (CRF) and on the Overdose eCRF module.

An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.6.7) and **within 30 days** for all other overdoses.

8.8 Human Biological Samples

Human Biological Samples obtained as part of this study will be stored and destroyed as per local laboratory practice.

8.8.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.8.2 Pharmacodynamics

Samples for the analysis of peripheral blood eosinophils and total IgE will be analyzed in a local/site laboratory.

8.8.2.1 Collection of Samples

Blood samples will be collected for measurement of eosinophil counts and IgE at timepoints

specified in the SoA (Table 1).

For storage, re-use, and destruction of pharmacodynamic samples see Section 8.8 and Appendix D.

8.9 Human Biological Sample Biomarkers

Not applicable.

8.10 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

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

9.2 Sample Size Determination

The sample size of 400 participants is based on practical considerations and the ability to obtain at least 50 participants in major subgroups of interest: individuals who identify as Black/African American, adolescents, individuals with comorbid diagnosis of mild to moderate COPD, and individuals with a significant history of smoking.

To provide some context regarding the sample size for this study, the statistical power to detect a statistically significant difference between the exacerbation rates in the baseline and follow-up periods is shown in the table below by hypothetical true rate ratios and sample sizes, using a two-group test comparing incidence rates using the negative binomial model. Based on these values, the target sample size for effectiveness analyses is at least 100 participants with evaluable data. In order to assess the treatment effect in subgroups as set out in Phase 1 and Phase 2, the sample size of 400 subjects is proposed.

Table 5 Power Values Under Different Assumptions

Hypothetical "true" rate ratio	Sample size			
	50	**100**	**200**	**400**
0.4	87.38%	99.25%	100%	100%
0.5	67.39%	92.64%	99.79%	100%
0.6	44.02%	72.54%	95.14%	99.92%

Calculations assumed a pre-tezepelumab rate of 2.25 asthma exacerbations per person-year, a common dispersion parameter of 1.4, a significance level of 0.05, and a mean exposure time of a year.

It should be noted that the study is not powered to demonstrate differences in exacerbations between the pre-baseline period and the post-baseline period for subgroups due to the small sample sizes within the subgroups.

9.3 Populations for Analyses

The following populations are defined:

9.3.1 All Participants Analysis Set

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

9.3.2 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 will be analyzed irrespective of whether they prematurely discontinue, according to the intent-to-treat principle. Participants who withdraw from the study or die will be included up to the date of their study termination/death. All safety and efficacy analyses will be performed using the Full Analysis Set (FAS). For consistency, demographics and baseline characteristics will be presented using the FAS.

9.4 Statistical Analyses

The statistical analyses will be fully described in a SAP, as appropriate. Statistical analyses for this study will be conducted using SAS® v9.4 or latest version in a secure and validated platform.

The SAP will be finalized and signed off prior to first participant enrolled. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Descriptive summaries of all the endpoints will be presented for all participants in the FAS and for the relevant subgroups of interest. For most continuous endpoints, absolute values and change from baseline values will be summarized by timepoint. Numbers and proportions of responders will also be summarized for several of the endpoints. Continuous variables will be summarized using the mean, the standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Time to event data will be presented in a tabular format and graphically. Data will be listed in-participant-level data listings by timepoint.

No formal hypothesis will be tested in this study, and no multiplicity adjustment will be applied in the statistical analysis. No imputation will be performed beyond the approach defined for outcome measures. Imputation for partial dates will be detailed in the SAP document.

In general, all data up to Week 52 will be included in the statistical analysis, even if a participant discontinues treatment or initiates other non-biologic medication for asthma. If a participant initiates therapy with another biologic for treatment of asthma, all data after the initiation of treatment will be removed from the analyses.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

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

- Primary endpoint:
  - 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)– discrete number
  - 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)

The primary objective of this study is 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 will be achieved by performing an analysis of the incidence of exacerbations 12 months after the index date compared to the baseline period (the 12 months prior to the index date). The annual exacerbation rate is 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, will not be included in the calculation of time at risk for an exacerbation.

Any asthma exacerbation that occurs 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 will be counted as the same exacerbation event. Further details on combining exacerbation events will be provided in the SAP.

For the primary analysis, the exacerbation rate will be analyzed using generalized estimating equations (GEE) model for repeated measures, using a logit link function. The response variable in the model will be the number of asthma exacerbations experienced by a participant over the specific period followed by a negative binomial distribution. The model will include covariates of time period (baseline, study period) and age. The logarithm of the time at risk for exacerbation will be used as an offset variable in the model to adjust for participants having different follow-up times during which the events occur. Unstructured variance-covariance matrix will be assumed. If the model fails to converge with unstructured matrix, then compound symmetry will be used. The annual asthma exacerbation rate ratio and corresponding 95% CI will be presented. If the assumptions for the GEE model are violated, other truncated models will be explored for sensitivity analyses. Further details will be provided in the SAP.

The supportive endpoints of the primary endpoint will be presented descriptively. The number and proportion of participants who experienced an asthma exacerbation, and those who completed 52-week study period following tezepelumab initiation with any reduction, at least 50% reduction, and 100% reduction in total number of asthma exacerbations will be displayed. Cumulative asthma exacerbation days over 52 weeks before (baseline period) and after initiation of tezepelumab (study period) will be summarized by descriptive statistics.

All primary endpoint analyses will be based on the FAS.

9.4.2.2 Secondary Endpoint(s)

The following outcomes are designed to support the secondary objectives of the study:

- Time to first asthma exacerbation

- Asthma exacerbations resulting in any hospitalizations, or ED/UC visits over 52 weeks before (baseline period) and after initiation of tezepelumab (study period)
  - Rate of asthma exacerbations associated with hospitalizations (only), ED/UC visits (only), or with hospitalizations or ED/UC visits over 52 weeks before (baseline period) and after initiation of tezepelumab (study period)
  - Proportion of participants with asthma exacerbations associated with hospitalizations or ED/UC visits over 52 weeks before (baseline period) and after initiation of tezepelumab (study period)– discrete numbers
  - Cumulative asthma exacerbationsdays associated with hospitalizations or ED/UC visits over 52 weeks before (baseline period) and after initiation of tezepelumab (study period)
- Absolute values at and changes from baseline (Visit 2 before the first dose of study intervention) to Visit 8 (6 months) and Visit 15 (12 months), respectively:
  - pre-BD FEV_1 (for pre-BD FEV_1, baseline maybe either Visit 1 or before the first dose of study intervention at Visit 2)
  - ACQ-6 score
  - AIRQ score
  - SGRQ score
- Proportion of pre-BD FEV_1 responders (defined as participants who achieve either at least 5% or 100 mL improvement from baseline (either Visit 1 or before the first dose of study intervention at Visit 2) at Visit 8 [6 months] and Visit 15 [12 months], respectively)
- Proportion of responders (participants who achieve ≥1 MCID, from Visit 2 at Visit 8 and Visit 15, respectively):
  - ACQ-6 scores
  - AIRQ scores
  - SGRQ scores
- Systemic corticosteroids (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 SCS use (> 30 consecutive days)
- 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 hospitalization

The time to first asthma exacerbation will be calculated and summarized graphically using Kaplan-Meier estimates.

Annual asthma exacerbation rate associated with hospitalizations only, ED/UC visits only, or with hospitalizations or ED/UC visits over 52 weeks, calculated in years as total number of exacerbations of interest divided by the total time at risk, will be summarized descriptively. Cumulative asthma exacerbation days associated with hospitalizations or ED/UC visits over 52 weeks before (baseline period) and after initiation of tezepelumab (study period) will be presented descriptively.

The number and proportion of participants who experienced an asthma exacerbation resulting in hospitalizations or ED/UC visits over 52 weeks, defined as responders (based on pre-BD FEV_1, ACQ-6, AIRQ, or SGRQ total scores), those who require any SCS use, and those who require longer-term SCS use (>30 consecutive days) will be summarized at Visit 8 and Visit 15.

For continuous secondary endpoints, absolute values and absolute (and relative if appropriate) changes from baseline (eg, pre-BD FEV_1, ACQ-6, AIRQ, SGRQ total scores) will be summarized by timepoint using descriptive statistics. In addition, the change from baseline in each endpoint will be analyzed using a model for repeated measures. The response variable in the model will be the change from baseline (absolute or percentage, as appropriate) at each scheduled visit at Visit 8 (6 months) and Visit 15 (12 months). Baseline value of the corresponding endpoint will be included in the model as a continuous covariate. Results from the model will be tabulated (least square mean with 95% CI) and presented graphically.

The asthma-related HRU events will be presented as number and percentages. The duration of asthma-related hospitalization will be summarized using descriptive statistics.

The annualized asthma exacerbation rates (all exacerbations, exacerbations associated with ED/UC visits and/or hospitalizations) and other endpoints related to exacerbations and HRU will be analyzed in subgroups specified in Table 2.

Further details of the analysis for these subgroups and remaining secondary endpoints will be provided in the SAP.

All secondary endpoint analyses will be based on the FAS.

9.4.2.3 Exploratory Endpoint(s)

The following outcomes are designed to support the exploratory objectives of the study:

- TSQM-9 score measured at 6 and 12 months after initiation of tezepelumab.
- CGI-C score measured at 6 and 12 months after initiation of tezepelumab.

- TNSS score measured at baseline (Visit 2 before the first dose of study intervention), 6 and 12 months after initiation of tezepelumab.
- SNOT-22 total score measured at baseline (Visit 2 before the first dose of study intervention), 6 and 12 months after initiation of tezepelumab (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).
- PGI-C score for COPD measured at 6 and 12 months after initiation of tezepelumab (only among participants with ongoing diagnosis of COPD prior to tezepelumab dosing at Visit 2).
- Mean change from baseline (Visit 2 before the first dose of study intervention) to Visit 8 (6 months) and Visit 15 (12 months), respectively:
  - TNSS score
  - SNOT-22 total score
  - Asthma trigger survey (Visit 15 only)
  - FPC composite score
- Absolute values of post-BD FEV_1 at Visit 8 (6 months) and Visit 15 (12 months), respectively.
- Change in FEV_1 from baseline (ie, either Visit 1 or before the first dose of study intervention at Visit 2) at Visit 8 (6 months; post-BD FEV_1) and Visit 15 (12 months; post-BD FEV_1), respectively.
- Proportion of responders (participants who achieve ≥1 MCID, from Visit 2 at Visit 8 (6 months) and Visit 15 (12 months), respectively):
  - TNSS score
  - SNOT-22 total score
- Proportion of participants who achieve clinical remission for the following time periods:
  - 6-months (Between Visit 2 to Visit 8)
  - 12-months (Between Visit 2 to Visit 15)
- The annualized asthma exacerbation rates (all exacerbations, exacerbations associated with ED/UC visits and/or hospitalizations) and other endpoints related to exacerbations and HRU will be analyzed in additional exploratory subgroups (sample permitting) as defined in the SAP.

All exploratory analyses will be based on the FAS.

Descriptive statistics for each endpoint at the baseline and post-baseline period will be generated to assess whether the magnitude of change differs based on the baseline value.

9.4.3 Safety

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug Dictionary.

The number and percentage of participants with SAEs, DAEs and AESIs will be presented by system organ class and preferred term. SAEs and AESIs will be summarized separately for the on-treatment and on-study periods. On-treatment SAEs, DAEs, and AESIs will also be summarised by causality/relatedness (as determined by the Principal Investigator).

Laboratory data will be summarised by summary statistics (means, medians, quartiles, ranges) of observed values. The incidence of clinically notable laboratory abnormalities will be listed.

All safety analyses will be based on the FAS.

9.5 Interim Analyses

One or more interim analyses may be conducted at any time at the discretion of the sponsor for the purpose of describing interim results and potentially supporting study publications. The results of the interim analysis will not be used to change any element of the study design and the study will continue regardless of the results of interim analysis. The interim analysis is not powered so it shouldn't be the reason of any study design changes. An additional SAP will be created to describe any interim analyses in more detail.

9.6 Data Monitoring Committee

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the Institutional Review Boards (IRB)/ Independent Ethics Committees (IEC), European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
  - European MDR 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

A Scientific Committee consisting of internal AstraZeneca and external experts (pulmonologists and allergists) who have been involved in the design of the clinical study will advise the sponsor on changes to the study design and provide recommendations on issues related to the study conduct, if required. In addition, the committee will be involved in the review and interpretation of the study results. The Scientific Committee will be governed by a charter, detailing roles and responsibilities and processes.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a studysite closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above

Adverse events (AEs) for **malignant tumors** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding Interactive Response Technology (IRT)/ Randomization and Trial Supply Management (RTSM) errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error

- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product.

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Management of Study Procedures During the COVID-19 Pandemic

C 1 Introduction

Safeguarding the health and wellbeing of our participants and ensuring the continued supply of our medicines to participants remains of paramount importance for AstraZeneca through the ongoing Coronavirus disease 2019 (COVID-19) outbreak.

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

C 2 Measures to Mitigate the Risks Associated with COVID-19

1. This study will start or resume enrolment only when the sponsor and Investigator deem it appropriate. In addition, the enrolment at a site level will only start or resume when local regulations and guidelines allow.
2. National laws and local recommendations regarding the pandemic will be strictly adhered to.
3. Site is encouraged to contact the participant within 1 day prior to a study visit to ask for signs and symptoms related to COVID-19.

C 3 Suspected COVID-19 After Screening

- **Participant is Severely Ill or Hospitalized**

If the participant becomes symptomatic after screening and has suspected COVID-19 (regardless of any SARS-CoV-2 test results that may be available), and is severely ill and/or hospitalized, the participant may temporarily (≤14 days), or permanently discontinue study intervention at the discretion of the site Investigator.

- **Participant is NOT Severely Ill or Hospitalized**

If the participant becomes symptomatic after screening and has suspected COVID-19 (regardless of whether any SARS-CoV-2 test results are available or not), and is NOT severely ill and/or hospitalized, the Investigator should determine if continuation of treatment with study intervention is in the best interest of the participant.

Regardless if study intervention is continued or not, the participant is encouraged to attend the study visits according to the schedule.

C 4 COVID-19 During the Study

- **Re-consent of Study Participants During Study Interruptions**

During study interruptions, it may not be possible for the participants to complete on-site study visits and assessments and alternative means for carrying out the visits and assessments may be necessary (eg, remote visits). Re-consent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in the Schedule of Activities (Section 1.3). Local and regional regulations and/or guidelines regarding re-consent of study participants should be checked and followed.

Visiting the study sites for the sole purpose of obtaining re-consent should be avoided.

- **Telemedicine Visit to Replace On-site Visit (Where Applicable)**

In this appendix, the term telemedicine visit refers to remote contact with the study participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, visits that are scheduled to be on-site may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medications to be reported and documented.

- **Data Capture During Telemedicine Visits**

Data collected during telemedicine visits will be captured by the qualified HCP from the study site.

Appendix D Maintenance Therapy Equivalence Table (medium, and high daily dosage of inhaled corticosteroids)

Table 6 Estimated Daily Doses for Inhaled Corticosteroids

Drug	**Total Daily Dose (mcg)**	
Inhaled Corticosteroid	**Medium**	**High**
Beclomethasone dipropionate (CFC)	> 500 - 1000	> 1000
Beclomethasone dipropionate (HFA)	> 200 - 400	> 400
Budesonide (DPI)	> 400 - 800	> 800
Budesonide suspension (nebules)	1000 - <2000	≥ 2000
Ciclesonide	> 160 - 320	> 320
Flunisolide	2000	> 2000
Fluticasone furoate (DPI, eg, Arnuity®, Ellipta®)	n.a.	200
Fluticasone propionate (DPI)	> 250 - 500	> 500
Fluticasone propionate (HFA)	> 250 - 500	> 500
Mometasone furoate	> 220 - 440	> 440
Triamcinolone acetonide	> 1000 - 2000	>2000
Inhaled Corticosteroid in ICS/LABA combination[b]	**Medium**	**High**
Beclomethasone dipropionate (eg, Fostair®)	400	> 400
Fluticasone furoate (eg, Relvar® Ellipta®, Breo® Ellipta®)	n.a.	184 - 200
Fluticasone propionate HFA (eg, Seretide®, Advair®)	> 320 - 460	> 460
Fluticasone propionate DPI (eg, Seretide Diskus®, Advair Diskus®)	>250 - 500	>500
Budesonide DPI (eg, Symbicort Turbuhaler®)	400 - < 800	800
Budesonide HFA (eg, Symbicort®)	320 - <640	640
Mometasone Furoate (eg, Dulera®)	400	800
Mometasone DPI (eg, Asmanex Twisthaler®)	330 - 440	> 440

[a] The ICS doses for the ICS/LABA combinations were derived from GINA 2020 and using prescribing information

[b] This a table of estimated clinical comparability. Categories of 'medium' and 'high' doses are based on published information and available studies, including direct comparisons where available.

Abbreviations: CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofluroalkane propellant; n.a. = not applicable.

Appendix E Anaphylaxis: Signs, Symptoms, and Management

E 1 Introduction

As with any antibody, allergic reactions to dose administration are possible. The WHO has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic IgE-mediated and non-IgE-mediated (eg, immunoglobulin G and immune complex mediated) and nonimmunologic (Johansson et al., 2004). The clinical criteria for defining anaphylaxis for this study are listed in Section 8.6.12. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample will be drawn from the participant as soon as possible after the event, at 60 minutes ±30 minutes after the event, and at discharge for analysis of serum tryptase.

E 2 Clinical Criteria for Defining Anaphylaxis

In adults, anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula).

AND AT LEAST ONE OF THE FOLLOWING:

a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b) Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

- Two or more of the following occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):

a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

- Reduced BP after exposure to known allergen for that participant (minutes to several hours): Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that participant's baseline value.

E 3 Signs, Symptoms, and Management of Acute Anaphylaxis

Anaphylaxis is an acute and potentially lethal multisystem allergic reaction in which some or all of the following signs and symptoms occur:

- Diffuse erythema
- Pruritus
- Urticaria and/or angioedema
- Bronchospasm
- Laryngeal edema
- Hypotension
- Cardiac arrhythmias
- Feeling of impending doom
- Unconsciousness
- Shock

Other earlier or concomitant signs and symptoms can include the following:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps, and bloating
- Light headedness
- Headache
- Uterine cramps
- Generalized warmth

E 4 Management of Acute Anaphylaxis

Immediate intervention

- Assessment of airway, breathing, circulation, and adequacy of mentation
- Administer epinephrine intramuscularly every 5 to 15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock, and unconsciousness.

Possibly appropriate, subsequent measures depending on response to epinephrine

a) Place participant in recumbent position and elevate lower extremities

b) Establish and maintain airway

c) Administer oxygen

d) Establish venous access

e) Normal saline intravenous for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

a) Consider epinephrine infusion

b) Consider H1 and H2 antihistamines

c) Consider nebulized β2 agonist (eg, albuterol [salbutamol]) for bronchospasm resistant to epinephrine

d) Consider systemic corticosteroids

e) Consider vasopressor (eg, dopamine)

f) Consider glucagon for participant taking a β-blocker

g) Consider atropine for symptomatic bradycardia

h) Consider transportation to an emergency department or an intensive care facility

i) For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

Adapted from Kemp et al., 2008.

Appendix F Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization 14155 and European MDR 2017/745 for clinical device research (if applicable).
- Both the Investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to the Tezepelumab APFS provided for use in the study

F 1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

- An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved.
- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

F 2 Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:

- Led to death
- Led to serious deterioration in the health of the participant, that either resulted in:
  - A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

  - A permanent impairment of a body structure or a body function.
  - Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
  - Chronic disease (MDR 2017/745).
- Led to foetal distress, foetal death, or a congenital anomaly or birth defect

Serious ADE (SADE) Definition

- A SADE is defined as an adverse medical device effect that has resulted in any of the consequences characteristic of an SAE.
- Any medical device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) Definition

An USADE (also identified as UADE in United States Regulations 21 CFR 813.3), is defined as a serious adverse medical device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

F 3 Definition of Medical Device Deficiency

A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

F 4 Recording and Follow-up of AE and/or SAE and Medical Device Deficiencies

AE, SAE, and Medical Device Deficiency Recording

- When an AE/SAE/medical device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/medical device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE/medical device deficiency form.

- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For medical device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a medical device deficiency. This includes any amendment to the medical device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/medical device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. “Severe” is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/medical device deficiency.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) in his/her assessment.
- For each AE/SAE/medical device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/medical device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Follow-up of AE/SAE/Medical Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE/SAE/medical device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other HCPs.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

F 5 Reporting of Medical Device SAEs and SADEs

- All medical device SAEs will be reported in accordance with Section 8.6.7.

NOTE: There are additional reporting obligations for SADEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any medical device deficiency that is associated with an SAE must be reported to AstraZeneca **within 24 hours** after the investigator determines that the event meets the definition of a medical device deficiency.
- In addition to the reporting process described in Section 8.6.13, the AstraZeneca Product Complaint Intake form will be used to capture details of the device and related deficiency.
- Facsimile transmission of the AstraZeneca Product Complaint Intake form is the preferred method to transmit this information to the Study Clinical Lead /SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the AstraZeneca Product Complaint Intake form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the AstraZeneca Product Complaint Intake form within the designated reporting time frames.
- AstraZeneca will review all medical device deficiencies and determine and document in writing whether they could have led to an SAE. These medical device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

Appendix G Abbreviations

Abbreviation or special term	Explanation
AAER	Annualized asthma exacerbation rate
ACQ-6	Asthma Control Questionnaire 6
ADE	adverse device effect
AE	adverse event
AESI	Adverse event of special interest
AIRQ	Asthma Impairment and Risk Questionnaire
APFS	accessorized pre-filled syringes
ATS/ERS	American Thoracic Society/ European Respiratory Society
BEC	blood eosinophil count
CFC	chlorofluorocarbon propellant
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CI	confidence interval
COA	clinical outcome assessment
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease of 2019
CRF	case report forms
CRO	contract research organization
CSP	clinical study protocol
CT	Computed tomography
DAE	adverse event leading to discontinuation of tezepelumab
DPI	Dry powder inhaler
eCRF	electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
EOT	end of treatment
FAS	full analysis set
FEIA	Fluorescent Enzyme Immunoassay
FDA	United States Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FeNO	Fractional Exhaled Nitric Oxide
FPC	frequent productive cough
FVC	forced vital capacity

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
GEE	Generalised estimating equations
GMP	Good Manufacturing Practice
HCP	health care professional
HFA	hydrofluroalkane
HIPAA	Health Insurance Portability and Accountability Act
HRU	healthcare resource utilization
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
IgE	immunoglobin E
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Study File
IxRS	interactive web/voice response system
LABA	long-acting β2 agonist
LAMA	long-acting muscarinic agonist
MCID	minimum clinically important difference
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
OCS	oral corticosteroids
PEF	peak expiratory flow
PGI-C	Patient's Global Impression of Change
PN	predicted normal
Post-BD	post-bronchodilator
Pre-BD	pre-bronchodilator
PRO	patient-reported outcomes
Q4W	every 4 weeks
RCT	randomized clinical trial
RTSM	randomization and trial supply management
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan

Abbreviation or special term	Explanation
SC	subcutaneous
SCS	systemic corticosteroids
SGRQ	St. George's Respiratory Questionnaire
SNOT-22	Sino-nasal outcome test
SoA	Schedule of Activities
SOP	standard operating procedure
TNSS	Total Nasal Symptom Score
TSLP	thymic stromal lymphopoietin
TSQM-9	Treatment Satisfaction Questionnaire from Medication
UC	Urgent care
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States Prescribing Information

Appendix H TEZSPIRE™ USPI

This is the current USPI at the time of the protocol finalization.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TEZSPIRE safely and effectively. See full prescribing information for TEZSPIRE.

TEZSPIRE™ (tezepelumab-ekko) injection, for subcutaneous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE
TEZSPIRE is a thymic stromal lymphopoietin (TSLP) blocker, human monoclonal antibody (IgG2λ), indicated for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. (1)

Limitations of Use:
- Not for relief of acute bronchospasm or status asthmaticus. (1)

DOSAGE AND ADMINISTRATION
- Administer by subcutaneous injection. (2)
- Recommended dosage is 210 mg administered once every 4 weeks. (2)

DOSAGE FORMS AND STRENGTHS
Injection:
- 210 mg/1.91 mL (110 mg/mL) solution in a single-dose glass vial. (3)
- 210 mg/1.91 mL (110 mg/mL) solution in a single-dose pre-filled syringe. (3)

CONTRAINDICATIONS
Known hypersensitivity to tezepelumab-ekko or excipients. (4)

WARNINGS AND PRECAUTIONS
- Hypersensitivity Reactions: Hypersensitivity reactions (e.g., rash, allergic conjunctivitis) can occur after administration of TEZSPIRE. Initiate appropriate treatment as clinically indicated in the event of a hypersensitivity reaction. (5.1)
- Risk Associated with Abrupt Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with TEZSPIRE. Decrease corticosteroids gradually, if appropriate. (5.3)
- Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before therapy with TEZSPIRE. If patients become infected while receiving TEZSPIRE and do not respond to anti-helminth treatment, discontinue TEZSPIRE until the parasitic infection resolves. (5.4)
- Vaccination: Avoid use of live attenuated vaccines. (5.5)

ADVERSE REACTIONS
Most common adverse reactions (incidence ≥ 3%) are pharyngitis, arthralgia, and back pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2021

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TEZSPIRE is indicated for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

Limitations of Use:

TEZSPIRE is not indicated for the relief of acute bronchospasm or status asthmaticus.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of TEZSPIRE is 210 mg administered subcutaneously once every 4 weeks.

Missed Dose Information

If a dose is missed, administer the dose as soon as possible. Thereafter, the patient can continue (resume) dosing on the usual day of administration. If the next dose is already due, then administer as planned.

2.2 Preparation and Administration Instructions

TEZSPIRE is intended for administration by a healthcare provider.

Each vial and pre-filled syringe contains a single dose of TEZSPIRE.

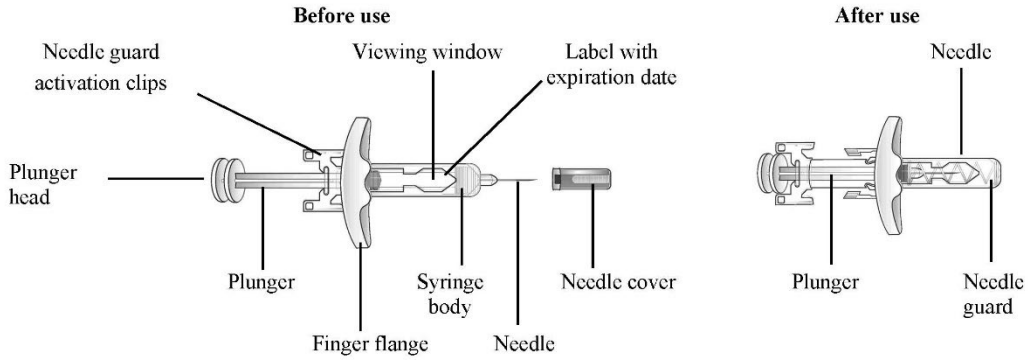
- Prior to administration, remove TEZSPIRE from the refrigerator and allow it to reach room temperature. This generally takes 60 minutes. Do not expose to heat and do not shake. Do not use if the security seal on the carton has been broken. Do not put back in the refrigerator once TEZSPIRE has reached room temperature. After removal from the refrigerator, TEZSPIRE must be used within 30 days or discarded *[see How Supplied/Storage and Handling (16)]*.
- Visually inspect TEZSPIRE for particulate matter and discoloration prior to administration. TEZSPIRE is a clear to opalescent, colorless to light yellow solution. Do not use TEZSPIRE if liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter. Do not use if the vial or pre-filled syringe has been dropped or damaged or if the expiration date has passed.
- Inject TEZSPIRE 210 mg (contents of one vial or one pre-filled syringe as described below) subcutaneously into the upper arm, thigh, or abdomen, except for the 2 inches (5 cm) around the navel. TEZSPIRE should not be injected into areas where the skin is tender, bruised, erythematous, or hardened. It is recommended to rotate the injection site with each injection.

Administration Instructions for Single-Dose Pre-filled Syringe

Refer to Figure 1 to identify the pre-filled syringe components for use in the administration steps.

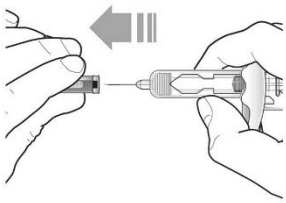
Do not remove the needle cover until Step 2 of these instructions when you are ready to inject TEZSPIRE. Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

Figure 1 TEZSPIRE Pre-filled Syringe Components

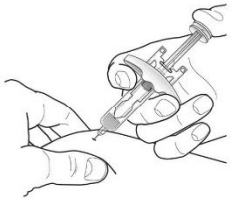


1. Grasp the syringe body to remove the pre-filled syringe from its tray. Do not grab the pre-filled syringe by the plunger.

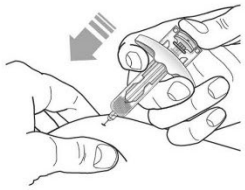
   The pre-filled syringe may contain small air bubbles; this is normal. Do not expel the air bubbles prior to administration.

2. 

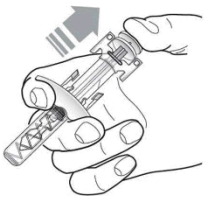
   Do not remove the needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover. You may see a drop of liquid at the end of the needle. This is normal.

3. 

   Gently pinch the skin and administer subcutaneously at approximately 45° angle into the recommended injection site (i.e., upper arm, thigh, or abdomen).

4. 

   Inject all of the medication by pushing in the plunger all the way until the plunger head is completely between the needle guard activation clips. This is necessary to activate the needle guard.

5. 
After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. Do not re-cap the pre-filled syringe.

6. Discard the used syringe into a sharps container.

3 DOSAGE FORMS AND STRENGTHS

Injection: a clear to opalescent, colorless to light yellow solution available as:

- 210 mg/1.91 mL (110 mg/mL) solution in a single-dose glass vial.
- 210 mg/1.91 mL (110 mg/mL) solution in a single-dose pre-filled syringe.

4 CONTRAINDICATIONS

TEZSPIRE is contraindicated in patients who have known hypersensitivity to tezepelumab-ekko or any of its excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., rash and allergic conjunctivitis) can occur following administration of TEZSPIRE *[see Contraindications (4) and Adverse Reactions (6)]*. These reactions can occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, consider the benefits and risks for the individual patient to determine whether to continue or discontinue treatment with TEZSPIRE.

5.2 Acute Asthma Symptoms or Deteriorating Disease

TEZSPIRE should not be used to treat acute asthma symptoms or acute exacerbations. Do not use TEZSPIRE to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with TEZSPIRE.

5.3 Risk Associated with Abrupt Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with TEZSPIRE. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.4 Parasitic (Helminth) Infection

Thymic stromal lymphopoietin (TSLP) may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if TEZSPIRE will influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with TEZSPIRE. If patients become infected while receiving treatment with TEZSPIRE and do not respond to anti-helminth treatment, discontinue treatment with TEZSPIRE until infection resolves.

5.5 Live Attenuated Vaccines

The concomitant use of TEZSPIRE and live attenuated vaccines has not been evaluated. The use of live attenuated vaccines should be avoided in patients receiving TEZSPIRE.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TEZSPIRE was based on the pooled safety population from PATHWAY and NAVIGATOR, which consists of 665 adult and pediatric patients 12 years of age and older with severe asthma who received at least one dose of TEZSPIRE 210 mg subcutaneously once every 4 weeks. The two placebo-controlled clinical trials were of 52 weeks duration. In addition, a similar safety profile was seen in a trial that enrolled 150 adult patients with severe asthma who required treatment with daily oral corticosteroids *[see Clinical Studies (14)]*.

Adverse reactions that occurred at an incidence greater than or equal to 3% and more common than in the placebo group from the pooled safety population (PATHWAY and NAVIGATOR) are shown in Table 1.

Table 1 Adverse Reactions with TEZSPIRE with Incidence Greater than or Equal to 3% and More Common than Placebo in Patients with Severe Asthma in the Pooled Safety Population (PATHWAY and NAVIGATOR)

Adverse Reaction	TEZSPIRE N=665 %	Placebo N=669 %
Pharyngitis*	4	3
Arthralgia	4	3
Back pain	4	3

* Pharyngitis (including Pharyngitis, Pharyngitis bacterial, Pharyngitis streptococcal and Viral pharyngitis)

Specific Adverse Reaction

Injection Site Reactions

In the pooled safety population, injection site reactions (e.g., injection site erythema, injection site swelling, injection site pain) occurred at a rate of 3.3% in patients treated with TEZSPIRE compared with 2.7% in patients treated with placebo.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including

neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies described below with the incidence of antibodies in other studies or to other tezepelumab products may be misleading.

In NAVIGATOR and an additional trial, anti-drug antibodies (ADA) were detected at any time in 29 (5%) out of 601 patients who received TEZSPIRE at the recommended dosing regimen during the 48 to 52-week study period. Of these 29 patients, 11 patients (2% of patients treated with TEZSPIRE) developed treatment-emergent antibodies and 1 patient (<1% of patients treated with TEZSPIRE) developed neutralizing antibodies. ADA titers were generally low and often transient. No evidence of ADA impact on pharmacokinetics, pharmacodynamics, efficacy, or safety was observed.

7 DRUG INTERACTIONS

No formal drug interaction studies have been performed with TEZSPIRE.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on TEZSPIRE use in pregnant women to evaluate for any drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Placental transfer of monoclonal antibodies such as tezepelumab-ekko is greater during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. In an enhanced pre- and post-natal development (ePPND) study conducted in cynomolgus monkeys, placental transport of tezepelumab-ekko was observed but there was no evidence of fetal harm following intravenous administration of tezepelumab-ekko throughout pregnancy at doses that produced maternal exposures up to 168 times the exposure at the maximum recommended human dose (MRHD) of 210 mg administered subcutaneously *[see Data]*.

The estimated background risk of major birth defects and miscarriages for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk:

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In the ePPND study, pregnant cynomolgus monkeys received tezepelumab-ekko from GD20 to GD22 (dependent on pregnancy determination), at the beginning of organogenesis, and once every 7 days until the end of gestation at doses that produced exposures up to 168 times that achieved with the MRHD (on an AUC basis with maternal intravenous doses up to 300 mg/kg/week). There were no tezepelumab-ekko related adverse effects on maternal health, pregnancy outcome,

embryo-fetal development, or neonatal growth and development up to 6.5 months of age. Tezepelumab-ekko crossed the placenta in cynomolgus monkeys and tezepelumab-ekko serum concentrations were 0.5- to 6.7-fold higher in infants relative to maternal animals.

8.2 Lactation

Risk Summary

There is no information regarding the presence of tezepelumab-ekko in human milk, its effects on the breastfed infant, or its effects on milk production. However, tezepelumab-ekko is a human monoclonal antibody immunoglobulin G2λ (IgG2λ), and immunoglobulin G (IgG) is present in human milk in small amounts. Tezepelumab-ekko was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TEZSPIRE and any potential adverse effects on the breastfed infant from TEZSPIRE or from the underlying maternal condition.

Data

Animal Data

In a prenatal and postnatal development study in cynomolgus monkeys, tezepelumab-ekko concentrations in milk were up to 0.5% of the maternal serum concentrations after intravenous administration of tezepelumab-ekko up to 300 mg/kg/week (168 times the exposures based on AUC achieved at MRHD). The concentration of tezepelumab-ekko in animal milk does not necessarily predict the concentration of drug in human milk.

8.4 Pediatric Use

The safety and effectiveness of TEZSPIRE for the add-on maintenance treatment of severe asthma have been established in pediatric patients aged 12 years and older *[see Adverse Reactions (6.1) and Clinical Studies (14)]*. Use of TEZSPIRE for this indication is supported by evidence from a total of 82 pediatric patients aged 12 to 17 years enrolled in NAVIGATOR and received treatment with TEZSPIRE 210 mg subcutaneously every 4 weeks (n=41) or placebo (n=41). Compared with placebo, improvements in annualized asthma exacerbation (rate ratio 0.70; 95% CI 0.34, 1.46) and FEV_1 (LS mean change versus placebo 0.17 L; 95% CI -0.01, 0.35) were observed in pediatric patients treated with TEZSPIRE. The safety profile and pharmacodynamic responses in pediatric patients were generally similar to the overall study population.

The safety and effectiveness in patients younger than 12 years of age have not been established.

8.5 Geriatric Use

Of the 665 patients with asthma treated with TEZSPIRE in clinical trials (PATHWAY and NAVIGATOR) for severe asthma, 119 patients (18%) were 65 years or older. No overall differences in safety or effectiveness of TEZSPIRE have been observed between patients 65 years of age and older and younger patients *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

11 DESCRIPTION

Tezepelumab-ekko, a thymic stromal lymphopoietin (TSLP) blocker, is a human monoclonal antibody immunoglobulin G2λ (IgG2λ) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Tezepelumab-ekko has a molecular weight of approximately 147 kDa.

TEZSPIRE (tezepelumab-ekko) injection is a sterile, preservative-free, clear to opalescent, colorless to light yellow solution for subcutaneous injection supplied in a single-dose vial or single-dose pre-filled syringe.

Each single-dose vial or pre-filled syringe delivers 1.91 mL containing 210 mg tezepelumab-ekko, glacial acetic acid (2.8 mg), L-proline (48 mg), polysorbate 80 (0.19 mg), sodium hydroxide, and water for injection. The pH is 5.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tezepelumab-ekko is a thymic stromal lymphopoietin (TSLP) blocker, human monoclonal antibody IgG2λ that binds to human TSLP with a dissociation constant of 15.8 pM and blocks its interaction with the heterodimeric TSLP receptor. TSLP is a cytokine mainly derived from epithelial cells and occupies an upstream position in the asthma inflammatory cascade.

Airway inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes, ILC2 cells) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in airway inflammation. Blocking TSLP with tezepelumab-ekko reduces biomarkers and cytokines associated with inflammation including blood eosinophils, airway submucosal eosinophils, IgE, FeNO, IL-5, and IL-13; however, the mechanism of tezepelumab-ekko action in asthma has not been definitively established.

12.2 Pharmacodynamics

In NAVIGATOR, administration of TEZSPIRE 210 mg subcutaneously every 4 weeks (n=528) reduced blood eosinophils counts, FeNO, IL-5 concentration and IL-13 concentration from baseline compared with placebo (n=531) with an onset of effect 2 weeks after initiation of treatment and sustained reduction on treatment to 52 weeks. TEZSPIRE caused a slow but progressive reduction in serum total IgE concentration throughout 52 weeks of treatment. Similar effects were seen in PATHWAY.

12.3 Pharmacokinetics

The pharmacokinetics of tezepelumab-ekko were dose-proportional following administration of a single subcutaneous dose over a dose range from 2.1 mg to 420 mg (0.01 to 2 times the recommended dose). With an every 4 weeks dosing regimen, tezepelumab-ekko achieves steady-state after 12 weeks and the accumulation ratio for C_{trough} is 1.86-fold.

Absorption

Following subcutaneous administration, the maximum serum concentration was reached in approximately 3 to 10 days. Based on population pharmacokinetic analysis, the estimated absolute bioavailability was approximately 77%. There was no clinically relevant difference in bioavailability when administered to different injection sites (abdomen, thigh, or upper arm).

Distribution

Based on population pharmacokinetic analysis, central and peripheral volume of distribution of tezepelumab-ekko were 3.9 L and 2.2 L, respectively, for a 70 kg individual.

Elimination

As a human monoclonal antibody, tezepelumab-ekko is eliminated by intracellular catabolism and there is no evidence of target-mediated clearance within the studied dose range. Based on population pharmacokinetic analysis, the estimated clearance for tezepelumab-ekko was 0.17 L/d for a 70 kg individual. The elimination half-life was approximately 26 days.

Metabolism

Tezepelumab-ekko is a human monoclonal antibody (IgG2λ) that is degraded by proteolytic enzymes widely distributed in the body and not metabolized by hepatic enzymes.

Specific Populations

Age, Sex, Race

Based on population pharmacokinetic analysis, age (12 to 80 years), sex and race (White, Black, Asian, Other) had no clinically meaningful effects on the pharmacokinetics of tezepelumab-ekko.

Body Weight

Based on population pharmacokinetic analysis, higher body weight was associated with lower exposure. However, the effect of body weight on exposure had no meaningful impact on efficacy or safety and does not require dose adjustment.

Patients with Renal impairment

No formal clinical studies have been conducted to investigate the effect of renal impairment on tezepelumab-ekko. The population pharmacokinetic analysis included 320 (23%) subjects with mild renal impairment and 38 (3%) subjects with moderate renal impairment. Tezepelumab-ekko clearance was similar in patients with mild renal impairment (estimated creatinine clearance 60 to 89 mL/min), moderate renal impairment (estimated creatinine clearance 30 to 59 mL/min) and those with normal renal function (estimated creatinine clearance $\geq$ 90 mL/min). Tezepelumab-ekko has not been studied in patients with severe renal impairment (estimated creatinine clearance $<$ 30 mL/min).

Patients with Hepatic impairment

No formal clinical studies have been conducted to investigate the effect of hepatic impairment on tezepelumab-ekko. Since tezepelumab-ekko is degraded by proteolytic enzymes widely distributed in the body and not metabolized by hepatic-specific enzymes, change in hepatic function is not expected to influence tezepelumab-ekko clearance.

Drug Interaction Studies

No formal drug interaction studies have been conducted with tezepelumab-ekko. Based on the population pharmacokinetic analysis, commonly co-administered asthma medications (leukotriene receptor antagonist, theophylline/aminophylline, oral and inhaled corticosteroid) had no clinically meaningful effect on tezepelumab-ekko clearance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic potential of tezepelumab-ekko. The malignancy risk in humans from an antibody that blocks TSLP ligand, such as tezepelumab-ekko, is currently unknown.

Male and female fertility was unaffected based upon no observed adverse histopathological findings in the reproductive organs and no changes in menstrual cycle or semen analysis in sexually mature cynomolgus monkeys that received tezepelumab-ekko for 26 weeks at subcutaneous doses up to 300 mg/kg/week (approximately 134 times the MRHD on an AUC basis).

14 CLINICAL STUDIES

The efficacy of TEZSPIRE was evaluated in two randomized, double-blind, parallel group, placebo-controlled clinical trials (PATHWAY [NCT02054130] and NAVIGATOR [NCT03347279]) of 52 weeks duration. The two trials enrolled a total of 1609 patients 12 years of age and older with severe asthma.

PATHWAY was a 52-week dose-ranging exacerbation trial that enrolled 550 adult patients with severe asthma who received treatment with tezepelumab-ekko 70 mg subcutaneously every 4 weeks, TEZSPIRE 210 mg subcutaneously

every 4 weeks, tezepelumab-ekko 280 mg subcutaneously every 2 weeks, or placebo subcutaneously. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or injectable corticosteroid treatment or 1 asthma exacerbation resulting in hospitalization in the past 12 months.

NAVIGATOR was a 52-week exacerbation trial that enrolled 1061 patients (adult and pediatric patients 12 years of age and older) with severe asthma who received treatment with TEZSPIRE 210 mg subcutaneously every 4 weeks or placebo subcutaneously every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or injectable corticosteroid treatment or resulting in hospitalization in the past 12 months.

In both PATHWAY and NAVIGATOR, patients were required to have an Asthma Control Questionnaire 6 (ACQ-6) score of 1.5 or more at screening and reduced lung function at baseline [pre-bronchodilator forced expiratory volume in 1 second (FEV_1) below 80% predicted in adults, and below 90% predicted in adolescents]. Patients were required to have been on regular treatment with medium or high-dose inhaled corticosteroids (ICS) and at least one additional asthma controller, with or without oral corticosteroids (OCS). Patients continued background asthma therapy throughout the duration of the trials. In both trials, patients were enrolled without requiring a minimum baseline level of blood eosinophils or FeNO.

The demographics and baseline characteristics of PATHWAY and NAVIGATOR are provided in Table 2 below.

Table 2 Demographics and Baseline Characteristics of Patients in PATHWAY and NAVIGATOR

	PATHWAY N=550	NAVIGATOR N=1059
Mean age (year) (SD)	52 (12)	50 (16)
Female (%)	66	64
White (%)	92	62
Black or African American (%)	3	6
Asian (%)	3	28
Hispanic or Latino (%)	1	15
Never smoked (%)	81	80
High-dose ICS use (%)	49	75
OCS use (%)	9	9
Mean number of exacerbations in previous year (SD)	2.4 (1.2)	2.8 (1.4)
Mean duration of asthma (years) (SD)	17 (12)	22 (16)
Mean baseline % predicted FEV_1 (SD)	60 (13)	63 (18)
Mean post-bronchodilator FEV_1 reversibility (%) (SD)	23 (20)	15 (15)
Mean baseline blood EOS count (cells/μL) (SD)	371 (353)	340 (403)
Positive serum specific IgE to any perennial allergen (%)*	46	64
Mean FeNO (ppb) (SD)	35 (39)	44 (41)

*in the FEIA panel

EOS, Eosinophils; FEIA, Fluorescent enzyme immunoassay; FeNO, Fractional exhaled nitric oxide; FEV_1, Forced expiratory volume in one second; ICS, Inhaled corticosteroid, IgE, Immunoglobulin E; OCS, Oral corticosteroid; ppb, Parts per billion; SD, Standard deviation.

The results summarized below are for the recommended TEZSPIRE 210 mg subcutaneously every 4 weeks dosing regimen.

Exacerbations

The primary endpoint for PATHWAY and NAVIGATOR was the rate of clinically significant asthma exacerbations measured over 52 weeks. Clinically significant asthma exacerbations were defined as worsening of asthma requiring the use of or increase in oral or injectable corticosteroids for at least 3 days, or a single depo-injection of corticosteroids, and/or emergency department visits requiring use of oral or injectable corticosteroids and/or hospitalization.

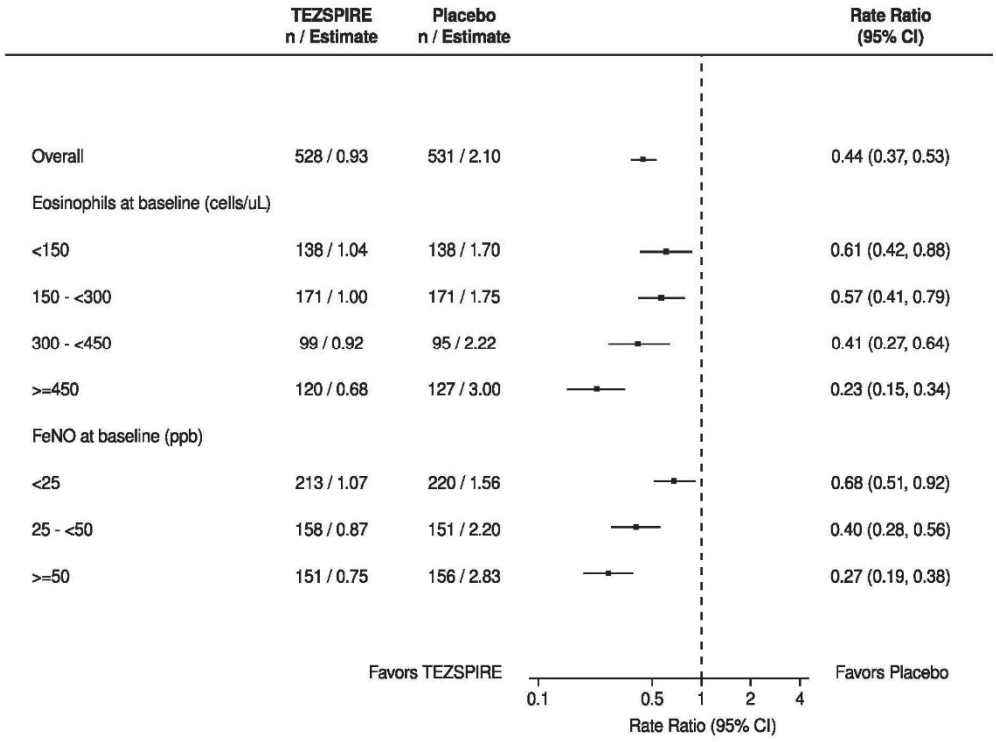
In both PATHWAY and NAVIGATOR, patients receiving TEZSPIRE had significant reductions in the annualized rate of asthma exacerbations compared to placebo. There were also fewer exacerbations requiring emergency room visits and/or hospitalization in patients treated with TEZSPIRE compared with placebo (Table 3).

Table 3 Rate of Clinically Significant Exacerbations Over 52 Weeks in PATHWAY and NAVIGATOR

Trial	Treatment	Exacerbations per year	
		Rate	Rate Ratio (95% CI)
Annualized Asthma Exacerbation Rate			
PATHWAY	TEZSPIRE (N=137)	0.20	0.29 (0.16, 0.51)
	Placebo (N=138)	0.72	
NAVIGATOR	TEZSPIRE (N=528)	0.93	0.44 (0.37, 0.53)
	Placebo (N=531)	2.10	
Exacerbations requiring emergency room visit/hospitalization			
PATHWAY	TEZSPIRE (N=137)	0.03	0.15 (0.04, 0.58)
	Placebo (N=138)	0.18	
NAVIGATOR	TEZSPIRE (N=528)	0.06	0.21 (0.12, 0.37)
	Placebo (N=531)	0.28	
Exacerbations requiring hospitalization			
PATHWAY	TEZSPIRE (N=137)	0.02	0.14 (0.03, 0.71)
	Placebo (N=138)	0.14	
NAVIGATOR	TEZSPIRE (N=528)	0.03	0.15 (0.07, 0.22)
	Placebo (N=531)	0.19	

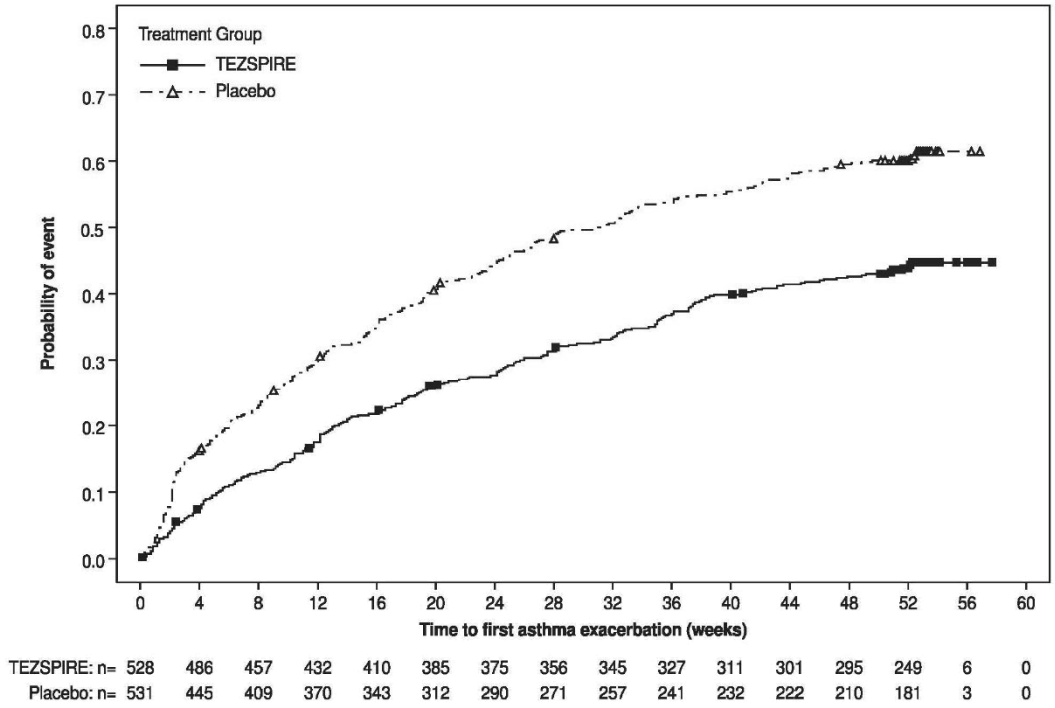
In NAVIGATOR, patients receiving TEZSPIRE experienced fewer exacerbations than those receiving placebo regardless of baseline levels of blood eosinophils or FeNO (Figure 2). Similar results were seen in PATHWAY.

Figure 2 **Annualized Asthma Exacerbation Rate Ratio Over 52 Weeks Across Different Baseline Biomarkers in NAVIGATOR**



The time to first exacerbation was longer for the patients receiving TEZSPIRE compared with placebo in NAVIGATOR (Figure 3). Similar findings were seen in PATHWAY.

Figure 3 **Kaplan-Meier Cumulative Incidence Curves for Time to First Exacerbation in NAVIGATOR**



Lung Function

Change from baseline in FEV_1 was assessed as a secondary endpoint in PATHWAY and NAVIGATOR. Compared with placebo, TEZSPIRE provided clinically meaningful improvements in the mean change from baseline in FEV_1 in both trials (Table 4).

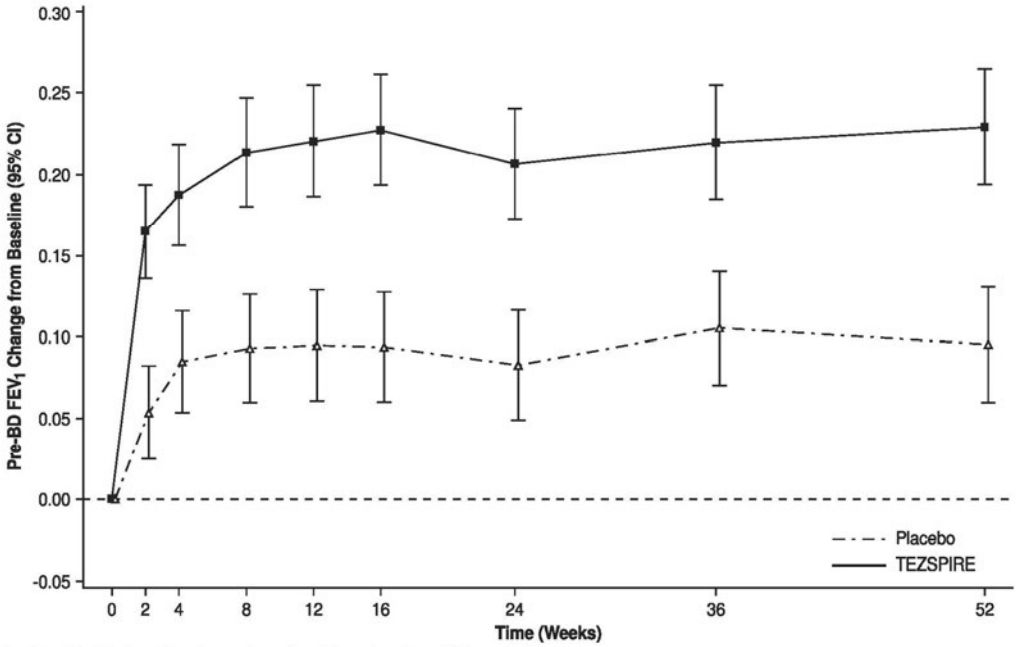
Table 4 **Mean Change from Baseline in Pre-Bronchodilator FEV_1 at End of Trial in PATHWAY and NAVIGATOR***

Trial	Treatment	LS Mean Change from Baseline (L)	Difference from Placebo (95% CI)
PATHWAY	TEZSPIRE (N=133)†	0.08	0.13 (0.03, 0.23)
	Placebo (N=138)†	-0.06	
NAVIGATOR	TEZSPIRE (N=527)†	0.23	0.13 (0.08, 0.18)
	Placebo (N=531)†	0.10	

*Week 52 in PATHWAY, Week 52 in NAVIGATOR
†Number of patients contributing to the full analysis (FA) with at least 1 change from baseline value

In NAVIGATOR, improvement in FEV_1 was seen as early as 2 weeks after initiation of treatment and was sustained through week 52 (Figure 4).

Figure 4 Mean Change (95% CI) from Baseline in Pre-Bronchodilator FEV_1 (L) in NAVIGATOR



Number of subjects with a change from baseline value at each time point

TEZSPIRE	527	514	523	518	510	510	497	483	471
Placebo	531	507	516	517	514	509	490	475	453

Patient Reported Outcomes

Changes from baseline in Asthma Control Questionnaire 6 (ACQ-6) and Standardized Asthma Quality of Life Questionnaire for ages 12 and older [AQLQ(S)+12] were also assessed as secondary endpoints in PATHWAY and NAVIGATOR. In both trials, more patients treated with TEZSPIRE compared to placebo had a clinically meaningful improvement in ACQ-6 and AQLQ(S)+12. Clinically meaningful improvement (responder rate) for both measures was defined as improvement in score of 0.5 or more at end of trial. In NAVIGATOR, the ACQ-6 responder rate for TEZSPIRE was 86% compared with 77% for placebo (OR=1.99; 95% CI 1.43, 2.76) and the AQLQ(S)+12 responder rate for TEZSPIRE was 78% compared with 72% for placebo (OR=1.36; 95% CI 1.02, 1.82). Similar findings were seen in PATHWAY.

Additional Trial

In a randomized, double-blind, parallel group, placebo-controlled clinical trial, the effect of TEZSPIRE (210 mg subcutaneously every 4 weeks) on reducing the use of maintenance OCS was evaluated. The trial enrolled 150 adult patients with severe asthma who required treatment with daily OCS (7.5 mg to 30 mg per day) in addition to regular use of high-dose ICS and a long-acting beta-agonist with or without additional controller(s). The primary endpoint was categorized percent reduction from baseline of the final OCS dose at Week 48 (≥90% reduction, ≥75% to <90% reduction, ≥50% to <75% reduction, >0% to <50 reduction, and no change or no decrease in OCS), while maintaining asthma

control. TEZSPIRE did not demonstrate a statistically significant reduction in maintenance OCS dose compared with placebo (cumulative OR=1.28; 95% CI 0.69, 2.35).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

TEZSPIRE (tezepelumab-ekko) injection is a sterile, preservative-free, clear to opalescent, colorless to light yellow solution supplied as a single-dose vial or single-dose pre-filled syringe with a fixed 27-gauge ½ inch needle with a needle cover. The needle cap and vial stopper are not made with natural rubber latex.

TEZSPIRE is available as:

- Single-Dose Vial: Carton contains one 210 mg/1.91 mL (110 mg/mL) in glass vial (NDC 55513-100-01)
- Single-Dose Pre-filled Syringe: Carton contains one 210 mg/1.91 mL (110 mg/mL) pre-filled syringe (NDC 55513-112-01)

Storage and Handling

Store refrigerated between 36°F to 46°F (2°C to 8°C). If necessary, TEZSPIRE may be kept at room temperature between 68°F to 77°F (20°C to 25°C) for a maximum of 30 days. Do not put back in the refrigerator once TEZSPIRE has reached room temperature. After removal from the refrigerator, TEZSPIRE must be used within 30 days or discarded.

Store TEZSPIRE in original carton to protect from light until time of use.

Do not freeze. Do not shake. Do not expose to heat.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., rash and allergic conjunctivitis) can occur following administration of TEZSPIRE *[see Contraindications (4) and Adverse Reactions (6)]*. These reactions can occur within hours of administration, but in some instances have a delayed onset (i.e., days). Instruct patients to contact their healthcare provider if they experience symptoms of an allergic reaction *[see Warnings and Precautions (5.1)]*.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that TEZSPIRE does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with TEZSPIRE *[see Warnings and Precautions (5.2)]*.

Risk Associated with Abrupt Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a healthcare provider. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms

and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.3)]*.

Administration of Vaccines

Instruct patients to inform the healthcare provider that they are taking TEZSPIRE prior to a potential vaccination *[see Warnings and Precautions (5.5)]*.

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US License No. 2059

At: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799

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PATIENT INFORMATION
TEZSPIRE™ (TEZ-SPY-ER)
(tezepelumab-ekko)
injection, for subcutaneous use

What is TEZSPIRE?

TEZSPIRE is a prescription medicine used with other asthma medicines for the maintenance treatment of severe asthma in people 12 years of age and older whose asthma is not controlled with their current asthma medicine.

TEZSPIRE helps prevent severe asthma attacks (exacerbations) and can improve your breathing.

TEZSPIRE is not used to treat sudden breathing problems. Tell your healthcare provider if your asthma does not get better or if it gets worse after you start treatment with TEZSPIRE.

It is not known if TEZSPIRE is safe and effective in children under 12 years of age.

Do not receive TEZSPIRE if you:

- are allergic to tezepelumab or any of the ingredients in TEZSPIRE. See the end of this Patient Information leaflet for a complete list of ingredients in TEZSPIRE.

Before you receive TEZSPIRE, tell your healthcare provider about all of your medical conditions, including if you:

- have ever had a severe allergic reaction (hypersensitivity).
- have a parasitic (helminth) infection.
- have recently received or are scheduled to receive any live attenuated vaccinations. People who receive TEZSPIRE should not receive live attenuated vaccines.
- are pregnant, think you may be pregnant, or plan to become pregnant. It is not known if TEZSPIRE may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if TEZSPIRE passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive TEZSPIRE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Do not change or stop your corticosteroid medicines or other asthma medicines unless your healthcare provider tells you to.

How will I receive TEZSPIRE?

- Your healthcare provider will give you TEZSPIRE in a healthcare setting.
- TEZSPIRE is injected under your skin (subcutaneously) 1 time every 4 weeks.
- If you miss an appointment, ask your healthcare provider when to schedule your next treatment.

What are the possible side effects of TEZSPIRE?

TEZSPIRE may cause serious side effects, including:

- **severe allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of allergic reaction:
  - rash
  - hives
  - breathing problems
  - red, itchy, swollen, or inflamed eyes

The most common side effects of TEZSPIRE include:

- sore throat (pharyngitis)
- joint pain (arthralgia)
- back pain

These are not all of the possible side effects of TEZSPIRE.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TEZSPIRE

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about TEZSPIRE that is written for health professionals.

What are the ingredients in TEZSPIRE?

Active ingredient: tezepelumab-ekko

Inactive ingredients: glacial acetic acid, L-proline, polysorbate 80, sodium hydroxide, and water for injection

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For more information, go to https://www.TEZSPIRE.com or call 1-800-236-9933.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 12/2021

Appendix I Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1, 24 January 2022

Overall Rationale for the Amendment

This amendment includes updates to the protocol from the approved USPI.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Throughout document	"Uncontrolled asthma" changed to "severe asthma", where needed.	To align with USPI language.	Non-substantial
Section 1.3: Schedule of Activities and Section 8.1.4.10 Patient's Global Impression of Change (PGI-C)	PGI-C removed from Visit 2.	Unable to measure a change prior to study intervention administration.	Non-substantial
Section 2: Introduction	Text added regarding approval of tezepelumab in the US.	Now that the USPI has been approved for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma, approval and date added.	Non-substantial
Section 2.2: Background and Section 2.3: Benefit/Risk Assessment	Citation of USPI added.	Approved USPI now available.	Non-substantial
Section 2.2: Background	Text regarding study initiation after US approval deleted.	No longer applicable; USPI is available.	Non-substantial
Section 3: Objectives and Endpoints, and Section 9.4.2.3: Exploratory Endpoints	Removed text "Change from baseline in" for PGI-C score in objectives, and aligned the description of the exploratory endpoint with this change.	No longer applicable; PGI-C assessment at baseline (Visit 2) was removed.	Non-substantial
Section 4.1: Overall Design	Text added regarding adequate enrolment of patients with comorbid nasal polyps.	Added as a population of interest.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-Substantial
Section 5.1: Inclusion Criteria	"Male or female" participant added.	To align with a protocol from the same development program.	Non-substantial
Section 8.1.4: Clinical Outcome Assessments (COAs)	"Handheld device" changed to "tablet device".	Clarification.	Non-substantial
Section 8.1.4.11: Qualitative Participant Experience Interview	Example online platform change from MS Teams to Zoom, and specified audio only.	Zoom would be more familiar to participants and clarity.	Non-substantial
Section 8.4: Total IgE and Specific IgE	Seasonal allergies added in addition to perennial allergies.	Clarification.	Non-substantial.
Section 10: Appendix G: TEZSPIRE USPI	Appendix added.	Actual label appended.	Non-substantial
Section 11: References	Citation for TEZSPIRE USPI added.	USPI approved.	Non-substantial

Abbreviations: IgE = immunoglobin E; study intervention = investigational product; PGI-C = Patient's Global Impression of Change; US = United States; USPI = United States Prescribing Information.

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