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Country(ies) of Study	United States
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Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Inc. and AstraZeneca AB
MAH Contact	

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

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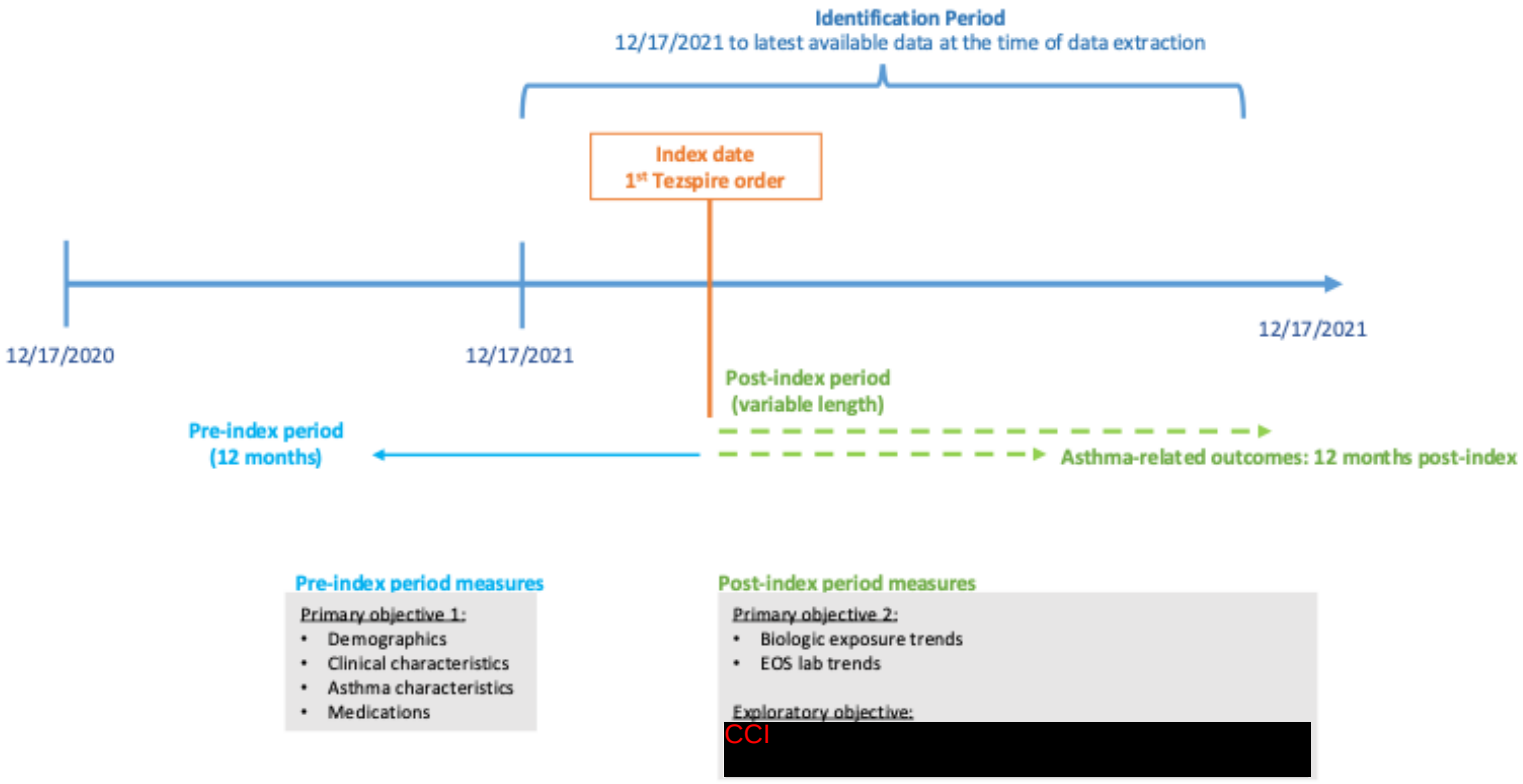
Study Design Schema



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2. List of Abbreviations

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AAER	Annualised asthma exacerbation rate
AIDS	Acquired immunodeficiency syndrome
BMI	Body mass index
CCI	Charlson Comorbidity Index
COPD	Chronic obstructive pulmonary disease
CPT	Current Procedural Terminology
ED	Emergency department
EMR	Electronic medical record
EOS	Eosinophil
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
HCO	Healthcare organization
HCPCS	Healthcare Common Procedure Coding System
HCRU	Healthcare resource utilization
HIV	Human immunodeficiency virus
ICD-9-CM	International Classification of Diseases, 9th revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th revision, Procedure Coding System
ICJME	International Committee of Medical Journal Editors
ICS	Inhaled corticosteroid
ICU	Intensive care unit
IDN	Integrated delivery network
IEC	Independent ethics committee
IgE	Serum immunoglobulin E
IQR	Interquartile range
IRB	Institutional Review Board
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LOINC	Logical observational identifiers names and codes
LTRA	Leukotriene receptor antagonist
OCS	Oral corticosteroid
SABA	Short-acting beta agonist
SAMA	Short-acting muscarinic antagonist
SD	Standard deviation
TSLP	Thymic stromal lymphopoietin
US	United States

3. Responsible Parties

Name	Professional Title	Role in Study	Affiliation	Email Address
PPD	VP, Research and Data Solutions	Strategic Lead	TriNetX	PPD
	Principal Research Scientist	Scientific Lead	TriNetX	
	Analyst	Primary Analyst	Statlog	
	Analyst	Validation Analyst	Statlog	
	Project Manager	Project Manager	TriNetX	
	Payer Evidence Director	Project Oversight	AstraZeneca	
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	Director, Health Economics Outcomes Research Lead	Project Oversight	Amgen	
	US Medical Affairs – Asset Lead	Project Oversight	Amgen	
	Global Medical Affairs Lead	Project Oversight	Amgen	
	Franchise Head, BioPharmaceuticals Medical, Respiratory	Project Oversight	AstraZeneca	

4. Abstract

- **Study Title**:

CROSSROADS-2: Clinical Characteristics, Treatment Patterns, and Treatment Outcomes Among Users of Tezspire (tezepelumab-ekko): An EMR study.

- **Study Background and Rationale**

Tezspire (tezepelumab-ekko), a monoclonal antibody targeting thymic stromal lymphopoietin (TSLP), was approved in December 2021 as an add-on maintenance treatment for patients aged 12 and over with severe asthma. There is limited real-world

data on the use of Tezspire (tezepelumab-ekko) and the outcomes of patients treated with Tezspire (tezepelumab-ekko).

- **Study Feasibility and Futility Considerations**

As of August 23, 2023, 1,011 Tezspire (tezepelumab-ekko) users were identified in TriNetX Dataworks-USA, of whom 583 had at least 2 Tezspire (tezepelumab-ekko) orders recorded.

- **Research Question and Objective(s)**

Objectives	**Endpoints**
Primary	
• To describe baseline demographics and clinical characteristics of new users of Tezspire (tezepelumab-ekko), overall and stratified by exacerbation history and biologic exposure.	• Demographic characteristics • Comorbidities • Clinical characteristics: asthma exacerbation history, vital signs, selected lab values, lung function measures • Asthma-related medications
• To describe the proportion of patients in the cohort that are biologic-naïve or biologic experienced at Tezspire initiation, and the proportion of patients in the cohort by blood eosinophil count categories at Tezspire initiation, by quarter.	• Biologic-naïve • Biologic-experienced • Blood eosinophils (EOS) o <150 cells/μL o 150 - <300 cells/μL o ≥300 cells/μL o ≥150 cells/μL o <300 cells/μL
Exploratory	
CCI [redacted]	

- **Hypothesis(es)/Estimation**

The primary objective is to describe baseline demographics and clinical characteristics of new users of Tezspire (tezepelumab-ekko) in a real-world population. This is a descriptive study with no *a priori* hypotheses.

- **Study Design/Type**

This is a retrospective cohort study that will include patients newly treated with Tezspire (tezepelumab-ekko) between December 17, 2021 and the most recent available data at the time of analysis.

- **Study Population or Data Resource**

The TriNetX Dataworks-USA network will be used for this study. Dataworks-USA is a de-identified, longitudinal electronic medical record (EMR)-derived dataset that includes outpatient and inpatient EMRs from 71 healthcare organizations (HCOs) (as of May 2025) across the United States (US). Data elements include demographics, diagnoses, medications, laboratory test results, vital signs, and procedures.

- **Summary of Patient Eligibility Criteria**

Inclusion criteria

1) Treatment with Tezspire (tezepelumab-ekko) between December 17, 2021 and the most recent available end date of the dataset (first medication order = index date).
2) 2 or more medication orders for Tezspire (tezepelumab-ekko) including the medication order at index
3) Age ≥ 12 years at the time of Tezspire (tezepelumab-ekko) initiation
4) At least one healthcare encounter prior to 365 days before index

    a. Office visit, inpatient admission, ED visit, diagnosis or procedure code, clinical measurement (e.g., blood pressure measurement), laboratory or diagnostic test, or medication order record

- **Follow-up**

The follow-up period (post-index period) will include a variable period, using all available follow-up time following index (Tezspire [tezepelumab-ekko] initiation) (Primary Objective 1), and CCI [redacted]

- **Variables**

Outcome Variable(s)

For Primary Objective 1, outcomes will include baseline characteristics, including demographics, comorbidities, clinical asthma characteristics, and asthma-related medications assessed during the pre-index period.

For Primary Objective 2, the proportion of patients who are biologic-naïve and biologic exposed at the index date (Tezspire initiation) will be described by the number of patients enrolled in the cohort, by quarter, who have asthma-related biologic exposure in the baseline period. Asthma-related biologic exposure includes any record of omalizumab, benralizumab, dupilumab, reslizumab, or mepolizumab in the pre-index period. Additionally, the proportion of patients enrolled in the cohort and with EOS lab results prior to index date (Tezspire

initiation) will be described, by quarter. The highest EOS measurement in the pre-index period will be used to assign EOS categories.

CCI [redacted]

Exposure Variable(s)

Not applicable.

- **Study Sample Size**

  There are no prespecified hypotheses for this study and a sample size/power calculation is not required. As of August 23, 2023 (prior to the first dataset download), 1,011 Tezspire (tezepelumab-ekko) users were identified in TriNetX Dataworks-USA, of whom 583 had at least 2 Tezspire (tezepelumab-ekko) orders recorded. As of May 17, 2025 (prior to the second dataset download), 4,199 Tezspire users were identified in the network, of whom 2,262 had at least two orders recorded.

- **Data Analysis**

  Data analysis will be descriptive. Categorical variables will be presented as frequencies (ns) and percentages (%) and continuous variables will be presented as mean, standard deviation (SD), median, interquartile range (IQR), and range (minimum, maximum).

5. Amendments and Updates

An amendment to the original protocol was conducted on June 6, 2025, due to insufficient sample size/patient accrual in the TriNetX Dataworks-USA network for the original primary objective (reduction of AAER). The major changes to the protocol include: 1) removal of treatment patterns (e.g., adherence, persistence) as Primary Objective 2; 2) addition of trends in biologic exposure and blood EOS labs as the new Primary Objective 2; 3) removal of reduction in AAER as Primary Objective 3 and subgroup analyses; and CCI [redacted]

Additional stratifications for Primary Objective 1 by biologic exposure and exacerbation history were included.

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Asthma is a chronic inflammatory lung disease of the airways estimated to affect over 400 million people globally.[1] Approximately 10% of individuals with asthma have severe asthma and continue to experience symptoms and exacerbations despite treatment with inhaled corticosteroids and long-acting β_2 agonists (LABAs). Severe, uncontrolled asthma is associated with increased hospitalizations and healthcare resource use, higher healthcare costs, poorer heath-related quality of life, and increased comorbidities.[2] Additionally, eosinophilic asthma, a subtype of asthma in which an increased number of airway and circulating eosinophils are present, accounts for approximately 80% of severe asthma cases and is associated with an increased

frequency of asthma exacerbations and reduced lung function.[3] Current treatment includes the use of biologic therapies as add-on therapies for patients suffering from severe, uncontrolled asthma.[4] However, the majority of current biologic agents are not suitable for patients with nonallergenic or noneosinophilic patients, which comprise approximately 20% of severe asthma patients.[5]

On December 17, 2021, Tezspire (tezepelumab-ekko) was approved in the United States (US) as an add-on maintenance treatment for adult and pediatric patients aged 12 years and older with severe asthma at the recommended dosage of 210 mg administered subcutaneously once every four weeks by a healthcare provider.[6]

Tezspire (tezepelumab-ekko) is a human monoclonal antibody that blocks thymic stromal lymphopoietin (TSLP). TSLP is an epithelial-cell-derived cytokine involved in multiple downstream processes involved in asthma pathophysiology.[7] In asthma patients, TSLP levels are correlated with asthma disease severity. TSLP drives both T2 inflammation of the airway and interactions between airway structural cells and immune cells.[8]

Several clinical trials have shown significant clinical benefits of treatment with Tezspire (tezepelumab-ekko) vs. placebo among asthma patients with uncontrolled asthma. The NAVIGATOR (rate ratio 0.44, 95% confidence interval [95% CI] 0.37-0.53) and PATHWAY trials (rate ratio 0.29, 90% CI 0.18-0.46) demonstrated that Tezspire (tezepelumab-ekko) was associated with significantly lower annual asthma exacerbation rates.[7,9] These effects were slightly larger in those with elevated eosinophil counts, indicating Tezspire (tezepelumab-ekko) as a treatment option for both eosinophilic and non-eosinophilic asthma. Additionally, the SOURCE study demonstrated that patients treated with Tezspire (tezepelumab-ekko) reduced oral corticosteroid use by up to 50% compared to placebo, although this result was not statistically significant.[10]

Tezspire (tezepelumab-ekko) is administered by a healthcare provider once every four weeks as a fixed-dose subcutaneous injection.[5,11] Tezspire (tezepelumab-ekko) is the sixth biologic to enter the US market for severe asthma, but unlike other biologics for the treatment of severe asthma, including Xolair, Fasenra, Dupixent, Cinqair, and Nucala, it does not have phenotypic or biomarker limitations. Compared to other biologic treatments, Tezspire (tezepelumab-ekko) is a broad-target biologic that suppresses asthma exacerbations in patients with poorly controlled, severe asthma regardless of blood eosinophil counts, fractional exhaled nitric oxide (FeNO), or the presence of sensitization to perennial allergens.[6] A recent network meta-analysis and simulated treatment comparison found that Tezspire (tezepelumab-ekko) had a lower annualized asthma exacerbation rate (AAER) than other biologic treatments.[12]

6.2 Rationale

Data on the real-world use, clinical characteristics, and asthma-associated outcomes of patients treated with Tezspire (tezepelumab-ekko) are limited. Although randomized trials are essential in drug evaluation, real-world evidence on the use and outcomes of Tezspire (tezepelumab-ekko) will support clinicians', patients', and other researchers' knowledge and confidence in implementing asthma treatments in the future. TriNetX, LLC and Amgen will conduct a retrospective cohort study to describe the characteristics of patients treated with Tezspire (tezepelumab-ekko) in the real-world setting using electronic medical record data (EMR). EMR data contains clinical variables that are essential for addressing the objectives of this study, including lab-based information (lung function tests, blood eosinophil counts), demographics, diagnoses, medication orders, and healthcare encounters. Additionally, this study will describe treatment patterns and asthma related clinical outcomes of patients initiating Tezspire

(tezepelumab-ekko). The present study is part of an ongoing CROSSROADS RWE program with studies to describe the real-world use of Tezspire (tezepelumab-ekko) in the US and associated clinical outcomes and healthcare resource utilization (HCRU). This is the first study assessing these outcomes using EMR data, which will complement results from claims database analyses assessing similar outcomes.

6.3 Feasibility and Futility Considerations

As of August 23, 2023 (prior to the first dataset download), 1,011 users of Tezspire (tezepelumab-ekko) were identified in Dataworks-USA, of whom 583 have at least 2 or more orders recorded. As of May 17, 2025 (prior to the second dataset download), 4,199 Tezspire users were identified in the network, of whom 2,262 had at least two orders recorded.

6.4 Statistical Inference (Estimation or Hypothesis[es])

Outcomes will be assessed descriptively, without hypothesis testing. Mean (standard deviation [SD]), median (interquartile range [IQR]), and range (min, max) will be calculated for continuous variables and frequencies and proportions for categorical variables. The cohort will be stratified by prior biologic exposure and exacerbation history, where applicable.

7. Research Question and Objectives

7.1 Primary

Primary Objective 1

- To describe the clinical characteristics of new users of Tezspire (tezepelumab-ekko).
    - Due to the descriptive nature of this study, no specific hypothesis will be tested.

Primary Objective 2

- To describe the proportion of patents in the cohort that are biologic-naïve or biologic experienced, and the proportion of patients in the cohort by blood eosinophil count categories, by quarter.
    - Due to the descriptive nature of this study, no specific hypothesis will be tested.

7.2 Exploratory

Exploratory Objective

CCI

[redacted]

8. Research Methods

8.1 Study Design

This is a non-interventional, descriptive retrospective cohort study of new users of Tezspire (tezepelumab-ekko). No comparative analyses will be performed and no hypotheses will be tested.

In the TriNetX Dataworks-USA database, patients who newly initiated Tezspire (tezepelumab-ekko) at the age of 12 or older in the United States will be identified. The first Tezspire (tezepelumab-ekko) initiation date for the patient will be defined as the index date for all objectives.

The index date will be between December 2021 (Tezspire [tezepelumab-ekko] launch) and the latest data available at the time of study execution. The pre-index period will be the 12-months preceding the index date. CCI [redacted]

For Primary Objective 1, the main outcomes of demographics, comorbidities, clinical asthma characteristics, and asthma-related medications will be assessed in the pre-index period.

For Primary Objective 2, the main outcomes including biologic exposure and blood EOS count categories will be assessed using in the pre-index period.

CCI [redacted]

8.2 Setting and Study Population

8.2.1 Study Period

The study period will be from December 17, 2020, to allow for a 12-month pre-index period from December 17, 2021 through most recent available data at the time of study execution. The study includes one data pull for Objective 1 (January 2024) and a second data pull for all objectives to allow accrual of enough follow-up and sample size (expected June 2025) (see Section 8.7.1).

8.2.2 Selection and Number of Sites

Not Applicable.

8.2.3 Subject/Patient/Healthcare Professional Eligibility

8.2.3.1 Inclusion Criteria

Inclusion criteria

1) Treatment with Tezspire (tezepelumab-ekko) between December 17, 2021, and the most recent available end date of the dataset (first medication order = index date).
2) 2 or more medication orders for Tezspire (tezepelumab-ekko) including the medication order at index
3) Age ≥ 12 years

4) At least one healthcare encounter prior to 365 days before index
    a. Office visit, inpatient admission, ED visit, diagnosis or procedure code, clinical measurement (e.g., blood pressure measurement), laboratory or diagnostic test, or medication order record

8.2.3.2 Exclusion Criteria

No exclusion criteria will be applied.

8.2.4 Matching

Not applicable.

8.2.5 Baseline Period

The baseline period (pre-index period) will be the 12-month period prior to the index event (patients' first Tezspire [tezepelumab-ekko] record).

8.2.6 Study Follow-up

Follow-up period (post-index period) will begin from index + day 1 through 12 months from the index event (patients' first Tezspire [tezepelumab-ekko] record).

8.3 Variables

8.3.1 Exposure Assessment

Not applicable.

8.3.2 Outcome Assessment

Outcomes are listed and defined below separately for Primary Objectives 1, 2, and the Exploratory Objective.

Outcomes for Primary Objective 1 will be baseline characteristics and include demographics, comorbidities, clinical asthma characteristics, and asthma-related medications, in the pre-index period.

Outcomes for Objective 2 include biologic exposure (omalizumab, benralizumab, dupilumab, reslizumab, or mepolizumab) and blood EOS labs in the study period (proportion of patients in the cohort, by quarter).

CCI [redacted]

8.3.2.1 Objective 1

Baseline characteristics are provided below in separate tables for demographics, comorbid conditions, clinical asthma characteristics, and respiratory medications. These characteristics will be assessed during the 12-month pre-index period. Comorbidities will be ascertained using International Classification of Diseases, Ninth/Tenth Revisions, Clinical Modification (ICD-9/10-CM) codes, lung function tests and labs will be ascertained using Logical Observation Identifiers Names and Codes (LOINCs), and medications will be ascertained using RxNorm, Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology (CPT), and International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS) codes. All codes are provided in the code list attached in Appendix A.

Demographic characteristics

Table 1. Demographic characteristics

Variable	Categories (if applicable)
Age at index, median (IQR)	N/A
Age at index, n (%)	12-<18 18-<30 30-<45 45-<60 >= 60
Sex, n (%)	Male Female Unknown
Race, n (%)	White Black Other Unknown
Ethnicity, n (%)	Hispanic Non-Hispanic Unknown
Geographic region, n (%)	Northeast South Midwest West Unknown

Clinical comorbidities and asthma characteristics

Table 2. Comorbidities in pre-index period

Variable	Definition
Body Mass Index (BMI), n (%)	Underweight (<18.5 kg/m^2) Normal (18.5 – 24.9 kg/m^2) Overweight (25.0 – 29.9 kg/m^2) Obese (≥30.0 kg/m^2) Unknown Defined via recorded BMI, calculated using recorded height and weight, or ICD-9/10 codes. If more than one is present, prioritization is as follows: recorded BMI, calculated BMI based on height and weight, ICD-9/10-CM codes. *Note. BMI is not available for patients <18 years.*
Charlson Comorbidity Index (CCI) score, mean (SD)	Ascertained and calculated using the Quan's algorithm for calculating CCI score[11]

Individual comorbidities comprising CCI, n (%)	In addition to the CCI score calculated above, each comorbidity within the CCI will be ascertained as a binary variable and reported as a frequency and proportion
Myocardial infarction	Presence of ICD-9/10-CM codes indicating diagnosis (see code list)
Congestive heart failure	
Dementia	
Chronic pulmonary disease	
Peripheral vascular disease	
Cerebrovascular disease	
Peptic ulcer disease	
Rheumatologic disease	
Mild liver disease	
Diabetes without chronic complications	
Diabetes with chronic complications	
Hemiplegia or paraplegia	
Renal disease	
Any malignancy except malignant neoplasm of skin	
Moderate/severe liver disease	
Metastatic solid tumor	
Acquired immunodeficiency syndrome/human immunodeficiency virus (AIDS/HIV)	
Type 2 inflammatory comorbidities, n (%)	
Allergic conjunctivitis	Presence of ICD-9/10-CM codes indicating diagnosis (see code list)
Allergic rhinitis	
Atopic dermatitis	
Eosinophilic esophagitis	
Chronic rhinosinusitis	
Nasal polyps	
Chronic spontaneous urticaria	
Autoimmune comorbidities, n (%)	
Rheumatoid arthritis	Presence of ICD-9/10-CM codes indicating diagnosis (see code list)
Psoriasis/psoriatic arthritis	
Multiple sclerosis	
System lupus erythematosus	
Systemic sclerosis or scleroderma	
Mixed connective tissue disease	
Respiratory comorbidities, n (%)	
Chronic obstructive pulmonary disease	Presence of ICD-9/10-CM codes indicating diagnosis (see code list)
Bronchiectasis	
Interstitial lung disease	

Cystic fibrosis	
Allergic bronchopulmonary aspergillosis	
Cryptogenic organizing pneumonia	
Sleep apnea	
Vocal cord dysfunction	
Other comorbidities, n (%)	
Anxiety/Depression	
Chronic spontaneous urticaria	
Dyslipidemia	
Gastroesophageal reflux disease (GERD)	
Hypertension	
Insomnia	
Ischemic heart disease	

Table 3. Clinical asthma characteristics in pre-index period

Variable	Definition
Prior exacerbation history, n (%)	Defined as having at least one of the three components listed in the subsequent rows. Exacerbations occurring < 14 days apart will be counted as the same exacerbation. Exacerbations occurring on the index date will be treated as pre-index exacerbations.
Exacerbation-related inpatient hospitalization	An inpatient hospitalization with an ICD-9/10 code indicating asthma exacerbation diagnosis (any diagnosis position) (with or without code for mechanic ventilation)
Exacerbation-related ED or urgent care visit with systemic corticosteroids	An ED visit or urgent care visit with an ICD-9/10 code indicating asthma exacerbation diagnosis (any diagnosis position) and an order for systemic corticosteroids (1 order of injectable steroids or oral corticosteroids [OCS]) within 7 days before or after the visit
Exacerbation-related outpatient visit with systemic corticosteroids	An outpatient visit (not including ED or urgent care) with an ICD-9/10 code indicating asthma exacerbation diagnosis (any diagnosis position) and an order for systemic corticosteroids (1 order of injectable steroids or OCS) within 7 days before or after the visit.

	For patients on maintenance OCS, the OCS order within 7 days must reflect an increase in dose for the outpatient visit to be counted as an exacerbation related visit. After exploring the data, if this if it is not feasible to assess an OCS dose increase, then patients on maintenance OCS may be excluded from objective 3.
Number of prior exacerbations, mean (SD)/median (IQR)/range	Defined as having at least one of the three components listed in the above rows. Exacerbations occurring < 14 days apart will be counted as the same exacerbation.
Lung function measures, mean (SD)/median (IQR)/range	
FEV1 (forced expiratory volume) (% of predicted FEV1)	Most recent measurement within the pre-index period. May be recorded directly or as separate FEV1 and predicted FEV1 values. Additional patients may have an FEV1 raw measure recorded (in liters) without a predicted FEV1. Calculation of the predicted FEV1 (based on equations provided by the European Respiratory Society), may be considered in order to convert to the percentage of the predicted FEV1.
FVC (forced vital capacity) (% of predicted FVC)	Highest measurement within the pre-index period Exploratory: Most recent measurement within the pre-index period. May be recorded directly or as separate FVC and predicted FVC values. Additional patients may have an FVC raw measure recorded (in liters) rather than a percentage of the predicted FVC. Calculation of the predicted FVC (based on equations provided by the European Respiratory Society) may be considered in order to convert to the percentage of the predicted FVC.
FEV1/FVC (%)	Highest measurement within the pre-index period Exploratory: Most recent measurement within the pre-index period.

FEV1 Pre-bronchodilation (L)	Highest measurement within the pre-index period Exploratory: Most recent measurement within the pre-index period.
FEV1 Post-bronchodilation (L)	Highest measurement within the pre-index period Exploratory: Most recent measurement within the pre-index period.
Other labs	
Blood eosinophils (EOS) (cells/μL), mean (SD)/median (IQR)/range	Highest measurement within the pre-index period Exploratory: Most recent measurement within the pre-index period.
Blood eosinophils (EOS) (cells/μL), n (%)	• <150 cells/μL • ≥150 to <300 cells/μL • ≥300 cells/μL • <300 cells/μL
Serum immunoglobulin E (IgE) (IU/mL), mean (SD)/median (IQR)/range	Highest measurement within the pre-index period Exploratory: Most recent measurement within the pre-index period.
Serum immunoglobulin E (IgE) (IU/mL), n (%)	• <100 IU/mL • ≥100 IU/mL • ≥100 to <400 IU/mL • ≥400 IU/mL • By quintiles
Serum specific IgE test (kU/L)	• ≤0.35 kU/L • >0.35 kU/L
Other labs, n (%)	
Fractional exhaled Nitric Oxide (FeNO)	FeNO values not available; performance of procedure within pre-index period will be reported (yes/no).
Baseline asthma status, n (%)	
Severe asthma, n (%)	1 or more of the following criteria: • ≥2 ORDERS for medium-to-high-dose inhaled corticosteroids (ICS) and long-acting beta-agonist (ICS/LABA) combination • ≥2 ORDERS for medium-to-high-dose ICS with additional controllers (eg, long-acting muscarinic antagonist [LAMA] or leukotriene receptor antagonists [LTRA]),

	which could come in the form of any of the following: • 2 ORDERS for medium-to-high-dose ICS + 2 ORDERS for LAMA (>= 14 days apart) • 2 ORDERS for medium-to-high-dose ICS + 2 ORDERS for LTRA >= 2 days apart (>= 14 days apart) • 2 ORDERS for medium-to-high-dose ICS + 1 ORDER for LAMA + 1 ORDER for LTRA (>= 14 days apart) • 2 ORDERS for medium-to-high dose ICS/LABA/LAMA combination • 1 ORDER for medium-to-high dose ICS/LABA/LAMA combination + 1 ORDER for medium-to-high dose ICS + 1 ORDER for LTRA or LAMA • OCS maintenance (the definition of OCS maintenance will be finalized after feasibility analysis of oral corticosteroids medication orders to be able to differentiate from continuous use to OCS burst; the proposed definition is > 6 orders for oral corticosteroids > 21 days apart [as days supply is not regularly available in Dataworks-USA EMR data]), • 1 or more ORDER for biologic therapy indicated for asthma (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab), with a diagnosis code for asthma during the pre-index period
Asthma control status, n (%)	
Uncontrolled	Meets one of the following: • ≥1 hospitalization encounter with a diagnosis of asthma as a diagnosis and corresponding record for mechanical ventilation or indication of intensive care unit (ICU) admission during the stay • ≥1 hospitalization encounter with a diagnosis of asthma without corresponding claim for mechanical ventilation during the stay • ≥2 ED, urgent care, or other outpatient visit claims carrying an asthma diagnosis code and receipt of systemic corticosteroids within 7 days
Sub-optimally controlled	Meets one of the following: • 1 ED, urgent care, or other outpatient visit encounter carrying an asthma diagnosis code and receipt of systemic corticosteroids within 7 days

	• ≥4 orders for a short-acting beta-agonist (SABA) at least 2 days apart
Controlled	Does not meet the criteria for uncontrolled or sub-optimally controlled listed above.

Medications

Table 4. Respiratory medications in pre-index period

Medication class	Medication agents
Medications, n (%)	
Short-acting beta agonists (SABAs)	Albuterol Levalbuterol Terbutaline Pirbuterol Metaproterenol
Short-acting muscarinic antagonist (SAMA)	Combivent (albuterol and ipratropium) Duoneb (albuterol and ipratropium)
Long-acting beta agonists (LABAs)	Formoterol Arformoterol (nebulized) Salmeterol Indacaterol Vilanterol Olodaterol
Inhaled corticosteroids (ICS)	Beclomethasone Budesonide Ciclesonide Fluticasone Mometasone Flunisode
Leukotriene receptor antagonists (LTRAs)	Montelukast Zafirlukast Zileuton
Long-acting muscarinic antagonists (LAMAs)	Tiotropium Umeclidinium Glycopyrrolate Revefenacin Aclidinium
Dual therapy inhaler (ICS/LABA)	Budesonide/Formoterol Fluticasone/Salmeterol Fluticasone/Vilanterol Mometasone/Formoterol Beclomethasone/formoterol
Triple therapy inhaler (ICS/LABA/LAMA)	Fluticasone/Vilanterol/Umeclidinium Budesonide/Glycopyrrolate/Formoterol
Cromolyn sodium	Cromolyn sodium
Theophylline	Theophylline

Macrolide	Erythromycin Roxithromycin Azithromycin Clarithromycin.
Other biologics used to treat asthma	Benralizumab Dupilumab Mepolizumab Omalizumab Reslizumab
Systemic corticosteroids	Dexamethasone Methylprednisolone Prednisolone Prednisone Beclomethasone Bethamethosone Hydrocortisone Triamcinolone

8.3.2.2 Objective 2

- Outcomes will include the proportion of patients in the cohort who are biologic-naïve or biologic-experienced, by quarter since Q4 2021 (start of cohort identification period). Patients will be assigned exposure status at index date based on asthma-related biologic exposure in the pre-index period. For each quarter, patients will be included in the denominator if they have been indexed on or before the last day of the quarter and will be censored at the last known encounter date. Asthma-related biologic exposure includes any record of omalizumab, benralizumab, dupilumab, reslizumab, or mepolizumab in during or prior to each quarter.
- Outcomes will also include the proportion of patients in the cohort, by quarter since Q4 2021, with blood EOS lab counts in the pre-index period. Patients will be assigned an EOS lab category based on the highest EOS lab value measurment in the pre-index period. For each quarter, patients will be included in the denominator if they have been indexed on or before the last day of the quarter and will be censored at the last known encounter date. Patients without an EOS lab measurement during the pre-index period will not be included in this analysis. EOS lab categories will include <150 cells/µL, 150 - <300 cells/µL, ≥300 cells/µL, or <300 cells/µL.
- Quarters will be defined for each year as follows:
    - Q1: January 1 – March 31
    - Q2: April 1 – June 30
    - Q3: July 1 – September 30
    - Q4: October 1 – December 31

8.3.2.3 Exploratory Objective

CCI

CCI

[redacted]

8.3.3 Covariate Assessment

Not applicable.

8.3.4 Subgroups

Not applicable.

8.3.5 Validity and Reliability

No comparisons or validation will be undertaken as part of this study.

8.4 Data Sources

The TriNetX Dataworks-USA network is a de-identified, longitudinal EMR-derived dataset, including outpatient and inpatient electronic medical records from 71 HCOs (as of May 2025) across the United States. These patient-level data are sourced from a global federated health research network with real-time updates (typically updated every 2 – 4 weeks). Network members include academic medical centers, integrated delivery networks (IDNs), specialty hospitals, and large specialty physician practices. The dataset has detailed clinical information available for over 90 million patients. Geographically, TriNetX healthcare organizations are well distributed across the US, except the Pacific Northwest.

Data elements are those in the fixed fields of the EMR (i.e., demographics, laboratory results, vitals, diagnoses, procedures, and prescribed medications), data captured via text mining of progress notes and other documents within the patient's record, and additional data linked at the patient level (e.g., mortality, genomics, tumor registry).

The data has medical encounters in the inpatient and outpatient setting that include demographics, diagnoses recorded, medications administered, prescriptions written, laboratory test results, vital signs, and procedures for each medical encounter and day of a hospital stay. All patient data in Dataworks-USA are harmonized to standard terminologies. Diagnoses are defined by ICD-9/-10-CM codes. Procedures are defined by CPT, HCPCS, and ICD-10-PCS codes. Medications ordered are defined by RxNorm Ingredient, CPT, HCPCS, and ICD-10-PCS medication codes. Lastly, laboratory test results are defined by LOINC codes.

Dataworks-USA is an ideal data source to address the study objectives for several reasons. First, the dataset represents a large patient population across the United States treated at a variety of institution types. Second, data within Dataworks-USA are regularly refreshed, ensuring that study findings reflect current practice. Third, the dataset contains clinical variables that are essential for addressing the objectives of this study: lung function tests, blood eosinophil counts, and other lab-based information in addition to variables normally found in EMR data sources (demographics, diagnoses, and medication orders, hospitalizations).

8.5 Study Size

As of August 23, 2023 (prior to the first dataset download), 1,011 Tezspire (tezepelumab-ekko) users were identified in TriNetX Dataworks-USA, of whom 583 had at least 2 Tezspire (tezepeluman-ekko) orders recorded. As of May 17, 2025 (prior to the

second dataset download), 4,199 Tezspire users were identified in the network, of whom 2,262 had at least two orders recorded.

8.6 Data Management

The data management approach is detailed below. All data collection and analyses will be overseen by the TriNetX scientific team. All data management will be conducted in SAS V9.4 (SAS, Cary, NC).

8.6.1 Obtaining Data Files

Not applicable.

8.6.2 Linking Data Files

Not applicable.

8.6.3 Review and Verification of Data Quality

All data collection and analyses will be overseen by the TriNetX scientific team experienced in retrospective, observational research using EMR data. Programming for this project will be conducted by the primary analyst and code reviewed by a separate validation analyst. For all data processing and analysis, the code, datasets, and results will be reviewed to reduce risk of errors.

8.7 Data Analysis

The methods of the data analysis are described for each objective below. For Objective 1, baseline characteristics will be assessed descriptively by calculating mean or median and frequencies and proportions for continuous and categorical variables, respectively. For Objective 2, the proportion of patients in the cohort, by quarter, will be described by biologic exposure and blood EOS levels. CCI [redacted] All analyses will be conducted in SAS V9.4 (SAS, Cary, NC).

8.7.1 Planned Analyses

8.7.1.1 Primary Analysis

The first analysis (i.e., first dataset download) will focus on the feasibility assessment and Primary Objective 1, describing the baseline clinical characteristics of new Tezspire (tezepelumab-ekko) users.

8.7.1.2 Final Analysis

To allow for the accrual of adequate follow-up time and sample size for new Tezspire (tezepelumab-ekko) users, the data will be downloaded for a second time several months after the initial analysis (expected June 2025), to be determined as part of the feasibility assessment. The final analysis will focus on the follow-up outcomes of Primary Objective 2 CCI [redacted] Additionally, the analysis for Primary Objective 1 will be re-run to have baseline characteristics for the updated cohort.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

All analyses will be descriptive, without hypothesis or statistical testing. Continuous measures will be reported as mean, SD, median, IQR (Q1, Q3) and range (min, max); categorical measures will be reported as count and percent.

Analyses will be stratified by previous biologic treatment status: biologic treatment naïve vs. previously treated with biologics in the pre-index period, where applicable, and by asthma exacerbation history: no exacerbations vs. ≥2 exacerbations in the pre-index period, where applicable.

All analyses will be conducted in SAS V9.4 (SAS, Cary, NC).

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

EMR data from the TriNetX Dataworks-USA network are generated from routine healthcare encounters within an “open” healthcare structure. Patients may receive all or a proportion of their care from healthcare providers within the HCO network. However, healthcare encounters which occur outside the HCO network will not be observed. Most contributing HCOs are large academic medical centers and IDNs with multiple affiliated sites of care. Using EMR data from large health systems, in some cases spanning large geographic areas, increases the likelihood of ascertaining data needed to classify and characterize the study cohort and to ascertain outcome data.

Where there is no ICD-9/10-CM, CPT, ICD-10-PCS, HCPCS, LOINC, or RxNorm code recorded, the patient will be classified as not having the respective comorbidity, baseline characteristic, HCRU, or outcome. This could lead to underestimates of the prevalence of certain conditions. To further mitigate the potential for missing data, eligibility requirements have been incorporated to restrict the study cohort to include only patients who regularly received care within the HCO network (i.e. requiring a healthcare encounter at least 12 months prior to the index date). In addition to improving the ascertainment of baseline data to characterize the study cohort, this also increases the probability that study cohort members will receive follow up care at these institutions.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

This will be a retrospective study utilizing secondary data thus no study enrollment is required. All identified patients who meet study criteria will be included. As of August 23, 2023 (prior to the first dataset download), 1,011 Tezspire (tezepelumab-ekko) users were identified in TriNetX Dataworks-USA, of whom 583 had at least 2 Tezspire (tezepelumab-ekko) orders recorded. As of May 17, 2025 (prior to the second dataset download), 4,199 Tezspire users were identified in the network, of whom 2,262 had at least two orders recorded.

8.7.2.3.2 Description of Subject/Patient Characteristics

Patient characteristics will be assessed during the 12-month pre-index period, including the index date. Categorical variables will be described using frequencies and percentages for categorical variables and means (SD), medians (IQR), and ranges (min, max) for continuous variables.

8.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

The methods for statistical analysis are described below for each objective. All analyses will be descriptive and will have no hypothesis or statistical testing. Continuous measures will be reported as mean (SD), median (IQR), and range (min, max); categorical measures will be reported as count and percent.

Primary Objective 1

For Primary Objective 1 analysis, the baseline characteristics listed in Section 8.3.2 will be assessed descriptively. Mean (SD), median (IQR), and range will be calculated for continuous variables. Frequencies (ns) and proportions (%) will be reported for categorical variables. See section 8.3.2 for details and definitions of the baseline characteristics.

Primary Objective 2

For Primary Objective 2, the proportion of patients in the cohort, by quarter, who are biologic-naïve vs. experienced, and who have blood EOS levels will be described. Frequencies (ns) and proportions (%) will be reported for categorical variables. See section 8.3.2.

Exploratory Objective

CCI [redacted]

8.7.2.5 Sensitivity Analysis

8.7.2.5.1 Subgroup Analysis

Not applicable.

8.7.2.5.2 Stratified Analysis

Results for Primary Objective 1 will be described overall and stratified by biologic exposure (biologic-naïve vs. biologic-experienced) and exacerbation history (no exacerbations in pre-index vs. ≥2 exacerbations in pre-index). CCI [redacted]

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable.

8.7.2.5.4 Other Sensitivity Analysis

Not applicable.

8.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Not applicable – safety data will not be collected or analyzed in this study.

8.8 Quality Control

There will be no primary data collection in this study. All data gathering and analysis will be overseen by the TriNetX study team experienced in the field of retrospective, observational research using EMR data. Programming will be conducted by the primary

analyst, with code review by a separate analyst. For all data processing steps, the secondary analyst will review the programming code along with all datasets and results (tables/figures). For each analysis step, code review will be used to reduce potential risk for programming errors.

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

Potential threats to internal validity include the potential for measurement error/misclassification and information bias, which are described below. The under-utilization of healthcare resources and informative censoring due to differential loss-to-follow-up (see section 8.9.1.3) during the COVID-19 pandemic may impose additional threats to the internal validity of the study.

8.9.1.1 Measurement Error(s)/Misclassification(s)

The TriNetX Dataworks-USA network is considered an 'open' network, meaning that patients may receive healthcare at HCOs outside of the network organization, which would not be observed in the EHR dataset and may lead to an under-reporting of certain outcomes. To mitigate this potential loss, patients are required to have at least one encounter within the network ≥365 days before index, ensuring that patients receive care at baseline and interact with the healthcare system.

8.9.1.2 Information Bias

Due to limited text mining from patients' medical records, it is possible some symptoms and comorbidities found in the provider notes or any other documents attached to the medical record may be missing in the data. Where there is no ICD-9/10-CM, CPT, ICD-10-PCS, HCPCS, LOINC, or RxNorm code recorded, the patient will be classified as not having the respective comorbidity, baseline characteristic, or outcome. This could lead to underestimates of the prevalence of certain conditions. While specific approaches to how data are recorded in the EMR or notes may vary across healthcare organizations and between providers, these differences are not expected to differentially impact the study cohorts.

8.9.1.3 Selection Bias

Stratification of results by asthma exacerbation history may mitigate any selection bias that would result in a bias towards those more likely to have a higher number of outcomes. However, this increases validity in comparing to the NAVIGATOR trial, which also required patients to have 2 or more exacerbations. Selection bias due to differential loss-to-follow-up (i.e., informative censoring) due to health plan disenrollment (and subsequent reduction in healthcare utilization) in certain populations during the COVID-19 pandemic may introduce bias.

8.9.1.4 Confounding

The study objectives will be purely descriptive in nature. Thus, confounding is not a consideration.

8.9.2 External Validity of Study Design

The underlying dataset for this study is sourced from the EMR of typically large healthcare organizations. Selection for the underlying dataset tends to follow trends of known healthcare-seeking behavior where women and older individuals seek care as well as trends of large organizations serving fewer rural communities. Results for study

objectives may be generalizable only to patients receiving care at academic medical centers or large community health centers within the United States. Geographically, TriNetX healthcare organizations are well distributed across the US, except the Pacific Northwest.

8.9.3 Analysis Limitations

This study will be descriptive in nature, without hypothesis or statistical testing. Due to the recency of Tezspire (tezepelumab-ekko) approval and data availability, there is a potential for reduced sample size. CCI [redacted] Due to within-patient variability, the natural course of disease, and measurement error, changes in outcomes may not be attributable to treatment. Regression to the mean may result from measurement error, within-patient variability and patient selection. Caution should be exercised when interpreting findings since causal inferences cannot be drawn from this study.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

Limitations of this study include: (1) Because of limited text mining from patients' medical records, it is possible some symptoms and comorbidities found in the provider notes or any other documents attached to the medical record may be missing in the data. Where there is no ICD-9/10-CM, CPT, ICD-10-PCS, HCPCS, LOINC, or RxNorm code recorded, the patient will be classified as not having the respective comorbidity, baseline characteristic, or outcome. This could lead to underestimates of the prevalence of certain conditions. While specific approaches to how data are recorded in the EMR or notes may vary across healthcare organizations and between providers, these differences are not expected to differentially impact the study cohorts. (2) In addition, patients may receive healthcare at multiple organizations such that the patient's complete healthcare profile and utilization will not be recorded in the EMR from the organization providing the patient's care for Tezspire (tezepelumab-ekko) administration. To mitigate this, inclusion criteria will be applied to increase the likelihood of including patients with all or a majority of their care captured in the dataset (requiring a healthcare encounter at least 12 months prior to the index date). (3) Though lung function tests are available in Dataworks-USA, they may have a varying degree of completeness among study patients. It is unclear if these missing data are random, thus patients with lung function test data may be different from those without it (e.g., differences in asthma severity).

8.10 Other Aspects

Not applicable.

9. Protection of Human Subjects

This study will be conducted in compliance with national requirements in the US for ensuring the rights of participants in non-interventional studies using de-identified data.

9.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Given that the data is de-identified and the retrospective nature of this study, IRB approval is not deemed necessary. The data from TriNetX is permitted to be in research and publications.

9.2 Subject/Patient Confidentiality

Not applicable – all data in TriNetX databases are de-identified.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

9.3 Subjects Decision to Withdraw

Not applicable – all data in TriNetX databases are de-identified.

10. Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from TriNetX Dataworks-USA, a global federates network of EMR data, and no safety data will be collected.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. When Amgen amends the protocol and distributes the protocol amendment to the sites, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement.

12. Plans for Disseminating and Communicating Study Results

12.1 Publication Policy

Study results will be submitted for publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.

- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

13. References

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14. Appendices

Appendix A. List of Stand-alone Documents

<<Documents listed in Appendix A can be maintained separately from the study protocol. They should be clearly identifiable and be provided on request.>>

<<Please indicate "None" if there is no document or list documents in the table as indicated below.>>

No.	Document Reference Number	Date	Title
1	*Number*	*Date*	*Codelist*
2	*Number*	*Date*	*Text*
...	*Number*	*Date*	*Text*

<<Code list>>