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| **Title** | CROSSROADS-2: Clinical Characteristics, Treatment Patterns, and Treatment Outcomes Among Users of Tezspire: An EMR study |
| **Protocol version identifier** | 1.0 |
| **Date of last version of the protocol** | 22 September 2023 |
| **EU Post Authorization Study (PAS) Register No** | NA |
| **Active Substance** | Tezspire (tezepelumab-ekko) |
| **Medicinal Product** | Tezspire (tezepelumab-ekko) |
| **Device** | NA |
| **Product Reference** | NA |
| **Procedure Number** | NA |
| **Joint PASS** | No |
| **Research Question and Objectives** | The objectives of this study are:<br>To describe the clinical characteristics of new users of Tezspire (tezepelumab-ekko).<br><br>To describe the treatment patterns of new users of Tezspire (tezepelumab-ekko) at 6 and 12 months after treatment initiation.<br><br>To assess and describe asthma outcomes of new users of Tezspire (tezepelumab-ekko) at 6 and 12 months after treatment initiation. |
| **Country(ies) of Study** | United States |
| **Author** | PPD , PharmD, PhD<br>Principal Research Scientist, TriNetX, LLC<br><br>PPD , MSc<br><br>PPD , PhD<br><br>PPD , PhD |

**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.

| Protocol Version | Date of Protocol | Page Header Date |
|---|---|---|
| Original, Version 1.0 | 22 September 2023 | 22 September 2023 |

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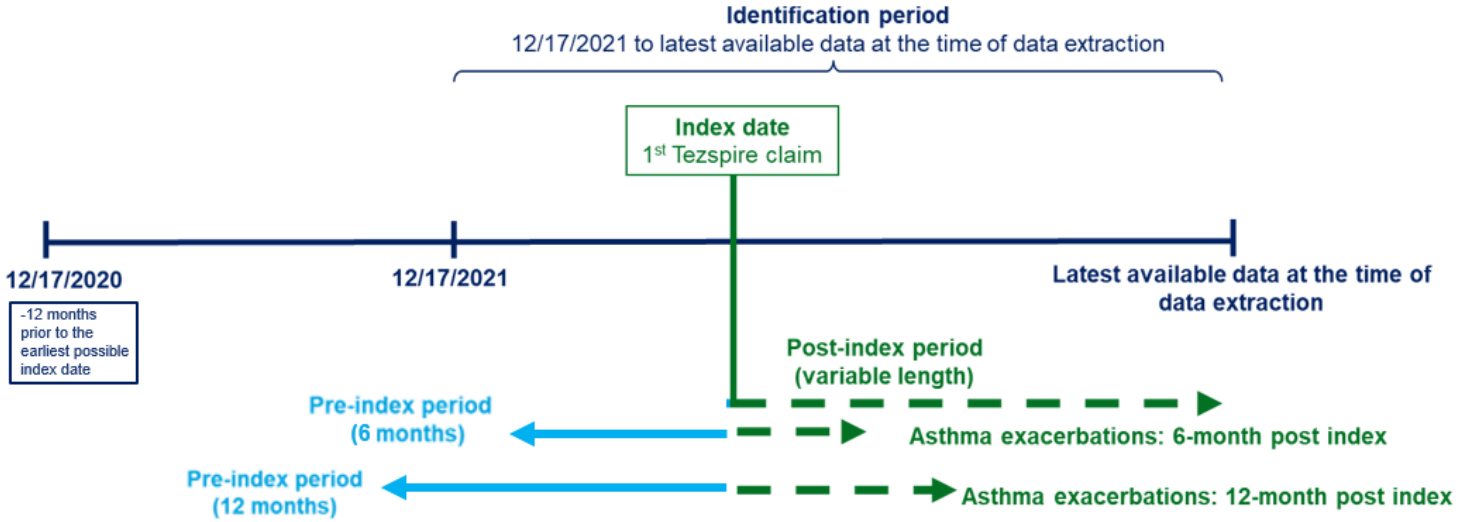
## Study Design Schema




**Pre-index period measures**

Primary objective 1:

- Demographics
- Clinical characteristics
- Prior asthma treatments
- Pre-index exacerbations
- Exacerbation related HCRU

**Post-index period measures**

Primary objective 2:

- Adherence
- Persistence
- Switching patterns

Primary objective 3:

- Post-index asthma exacerbations
- **Reduction in AAER in the post-index period compared to the pre-index period**

## 1. Table of Contents

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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 |
| GINA | Global Initiative for Asthma |
| HCO | Healthcare organization |
| HCPCS | Healthcare Common Procedure Coding System |
| HCRU | Healthcare resource utilization |
| HIV | Human immunodeficiency virus |
| ICD-9-CM | International Classification of Diseases, 9$^{th}$ revision, Clinical Modification |
| ICD-10-CM | International Classification of Diseases, 10$^{th}$ revision, Clinical Modification |
| ICD-10-PCS | International Classification of Diseases, 10$^{th}$ 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 |
| PDC | Proportion of days covered |
| 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 | CSO, RWE Consulting | Strategic Lead | TriNetX | PPD |
| | Principal Research Scientist | Scientific Lead | TriNetX | |
| | Analyst | Primary Analyst | Statlog | |
| | Analyst | Validation Analyst | Statlog | |
| | Project Manager | Project Manager | TriNetX | |
| | Project Manager | Project Manager | TriNetX | |
| | Research Assistant | Research Assistant | TriNetX | |
| | Payer Evidence Director | Project Oversight | AstraZeneca | |
| | Associate Scientist | Project Oversight | Amgen | |
| | 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). | • Demographic characteristics<br>• Comorbidities<br>• Clinical characteristics: asthma exacerbation history, vital signs, selected lab values, lung function measures<br>• Asthma-related medications |
| • To describe the treatment patterns of new users of Tezspire (tezepelumab-ekko) at 6 and 12 months after treatment initiation. | • Adherence<br>• Persistence<br>• Switching to other biologic treatments<br>• Discontinuation |
| • Among on-treatment patients[a] without evidence of use of other asthma biologics during the pre-index period:<br>  • To assess the reduction of asthma exacerbations resulting in hospitalizations, emergency visits, or outpatient visits after initiation of Tezspire (tezepelumab-ekko) (post-index period) compared to the pre-index period. | • Reduction of annualized asthma exacerbation rate (AAER) compared to the pre-index period |
| **Exploratory** | |

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- **Hypothesis(es)/Estimation**

The primary objective is to describe how treatment with Tezspire (tezepelumab-ekko) is associated with a reduction in the AAER among a real-world population. The specific hypothesis being tested is that treatment with Tezspire (tezepelumab-ekko) reduces the AAER compared to the pre-index period. Generalized estimating equations will be used to compare the AAER between the pre- and post-index time periods.

- **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 60 healthcare organizations (HCOs) across the United States (US). Data elements include demographics, diagnoses, medications, laboratory test results, vital signs, and procedures.

- **Summary of Patient Eligibility Criteria**

**Primary Objective 1**
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

**Primary Objective 2**
All four inclusion criteria identified for Primary Objective 1

**Primary Objective 3**
All four inclusion criteria identified in Primary Objective 1 and Primary Objective 2 **and**

5) Patients with no evidence of biologics during the pre-index period
6) Patients with 2 or more asthma exacerbations in pre-index period
7) Adherence to Tezspire (tezepelumab-ekko), defined as having at least 5 orders during the 6-month follow-up and at least 10 orders during the 12-month follow-up. Exploratory analysis will assess the AAER reduction using an alternative definition of 4 orders during the 6-month follow-up and 8 orders during the 12-month follow-up.

- **Follow-up**

  The follow-up period (post-index period) will be 12-months following index (Tezspire [tezepelumab-ekko] initiation).

- **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, outcomes will include measures of adherence, persistence, and discontinuation of Tezspire (tezepelumab-ekko) use in the follow-up period. Additionally, switches to other treatments will be described during the follow-up period.

  For Primary Objective 3, outcomes will include reduction in AAER among patients with no evidence of biologic use in the pre-index period.

  For Exploratory Objectives, outcomes will include reduction in AAER, exacerbation-associated HCRU measures, medication use, lung function measures and blood eosinophil counts assessed during the follow-up period.

  *Exposure Variable(s)*
  Not applicable.

- **Study Sample Size**

  To estimate the required sample size to assess AAER reduction in Objective 3, paired t-test calculations were performed assuming reductions of 10%, 20%, 40%, and 60%, preliminary AAER data from the TriNetX Dataworks-USA Network, and assuming a 0.2 correlation and 85% power.[13] In order to detect reductions in AAERs of 10%, 20%, 40%, and 60%, a sample of 1,711, 242, 37, and 9 patients would be required, respectively. 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. An initial feasibility assessment will be completed to ensure sufficient Tezspire (tezepelumab-ekko) users are identified for each objective analysis. A before and after Tezspire (tezepelumab-ekko) analysis using pooled NAVIGATOR (a Tezspire phase 3 multicenter, randomized, placebo-controlled study) and PATHWAY (a Tezspire phase 2b multicenter, randomized, placebo-controlled study) showed a 74% AAER reduction.

- **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). Generalized estimating equations will be used to compare the AAER between the pre- and post-index time periods.

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