Title	CROSSROADS-1: Treatment Outcomes among Tezspire Users: A Claims Data Study
Protocol version identifier	Version 2.0
Date of last version of the protocol	19 June 2023
EU Post Authorization Study (PAS) Register No	NA
Active Substance	<<active substance of studied product>>
Medicinal Product	Tezepelumab
Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	Assess the reduction of asthma exacerbations resulting in hospitalizations, emergency visits, or outpatient visits and the reduction in exacerbation related health care resource use after initiation of Tezspire (post-index period) compared to the pre-index period
Country(ies) of Study	United States
Author	Amgen: PPD One Amgen Center Drive, Thousand Oaks, California 91320 United States Phone: PPD IQVIA: PPD IQVIA, One IMS Drive Plymouth Meeting, PA 19462 PPD

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

Protocol Version	Date of Protocol	Page Header Date
Original Protocol, Version 1.0	19 June 2023	19 June 2023
Amendment 1, Version 2.0	05 January 2024	05 January 2024

Confidentiality Notice

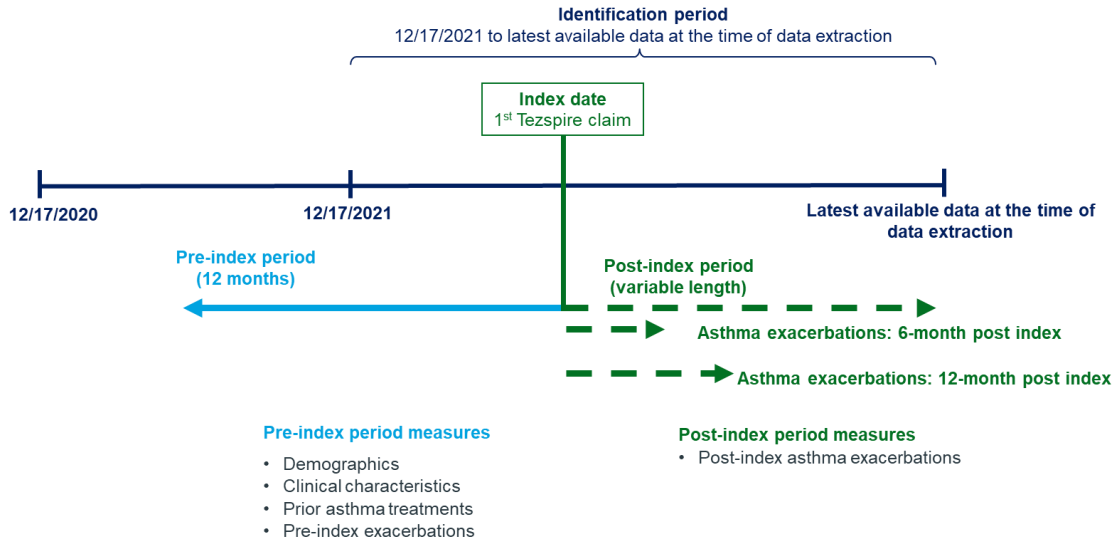
This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the Institutional Review Board/Independent Ethics Committee/Institutional Scientific Review Board or equivalent, as applicable.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the research without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: Amgen's general number in the US (1-805-447-1000*).*

Study Design Schema [Required]



1. Table of Contents

CCI

[redacted]

CCI

[redacted]

2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
CCI	Charlson Comorbidity Index
Dx	Open-source Medical Claims Database
ED	Emergency Department
FDA	Food and Drug Administration
GINA	Global Initiative for Asthma
HCPCS	Healthcare Common Procedure Coding System
HEOR	Health Economics & Outcomes Research
HIPAA	Health Insurance Portability & Accountability Act
ICS	Inhaled Corticosteroid
IV	Intravenous
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LRx	Open-source Pharmacy Claims Database
LTRA	Leukotriene Receptor Antagonists
NDC	National Drug Code
SABA	Short-Acting Beta-Agonist
SAMA	Short-Acting Muscarinic Antagonist
SD	Standard Deviation
SE	Standard Error
SOP	Standard Operating Procedure

3. Responsible Parties

Amgen:

PPD MS

PPD ; PhD

PPD ; PhD

PPD ; MD PhD

PPD ; MD

AstraZeneca:

PPD ; PharmD

PPD ; MD

IQVIA:

PPD , PhD

PPD , MPH

PPD , MPH

4. Abstract

- **Study Title**

CROSSROADS-1: Treatment Outcomes among Tezspire Users: A Claims Data Study

- **Study Background and Rationale**

In December 2021, AstraZeneca and Amgen received FDA approval for Tezepelumab-ekko (TezspireTM) for add-on maintenance treatment of adult and pediatric patients 12 years of age and older with severe asthma. Additional biologic asthma treatments available in the US market include omalizumab (Xolair®, approved in 2003), mepolizumab (Nucala®, approved in November 2015), reslizumab (Cinqair®, approved in March 2016), benralizumab (Fasenra®, approved in November 2017), and dupilumab (Dupixent®, approved for asthma in October 2018). Unlike other biologics for the treatment of severe asthma Tezspire does not have phenotypic or biomarker limitations. Tezspire 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.

This present study protocol outlines Phase 2 of an ongoing study. Phase 1 of the study (protocol 20221110) assessed patient characteristics and treatment patterns of early recipients of Tezspire using the IQVIA open-source medical and pharmacy claims data. Phase 2 will build on this study by describing treatment outcomes including reduction of asthma exacerbations and healthcare resource utilization among Tezspire users (comparing 6 before treatment with 6 after starting treatment and 12 months before treatment with 12 months after starting treatment). This study will help describe outcomes among Tezspire users, and in subgroups of interest in a real-world setting.

- **Study Feasibility and Futility Considerations**

A total of 1,873 patients were identified in PharMetrics Plus with at least 2 claims for Tezspire through August 2023. Counts are expected to increase by the time of data extraction.

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

Objectives	**Endpoints**
Primary	
Among those on-treatment patients[a] without evidence of use of other asthma biologics during the pre-index period: • To assess the reduction of asthma exacerbations resulting in hospitalizations, emergency visits, or outpatient visits after initiation of Tezspire (post-index period) compared to the pre-index period.	• Annualized asthma exacerbation rate (AAER) in the pre-index and post-index period • Annualized asthma exacerbation rate (AAER) reduction between the pre- and post-index periods (reported as percentage [%] reduction and as an absolute AAER difference)
Exploratory	
CCI [redacted]	

CCI

[redacted]

Hypothesis(es)/Estimation
The primary objective is to describe how treatment with Tezspire is associated with a reduction in the AAER among a real-world population. The specific hypothesis being tested is that treatment with Tezspire is associated with a reduction in the AAER. One-sided paired t-tests will be used to test this hypothesis.

- **Study Design/Type**

  This will be a retrospective cohort study conducted using the IQVIA PharMetrics Plus data. CCI [redacted]. Patients from the PharMetrics Plus will be linked to Prognos and Quest laboratory data for EOS/IgE values when possible (note: linkage will not be required for study inclusion).

- **Study Population or Data Resource**

  The study population consists of patients ≥12 years of age with ≥2 medical claim (NDC or HCPCS) or pharmacy claims (NDC) for Tezspire during the identification period (December 17, 2021 to 6 months prior to latest available data at the time of data extraction]) in the United States.

- **Summary of Patient Eligibility Criteria**

Patients will be included if the meet the following criteria:

- ≥1 claims for Tezspire (NDC or HCPCS) during the identification period (December 17, 2021 to 6 months before the end the latest available data at the time of data extraction)

  Index date = Date of the first claim for Tezspire during the identification period
- Patients with ≥1 claim with a diagnosis code for asthma in the pre-index period
- ≥12 years of age on the index date

- ≥2 claims for Tezspire (NDC or HCPCS) during the identification period (treatment patterns and baseline characteristics will be assessed in patients with at least 2 claims of Tezspire)

  Outcomes analysis (AAER) will be run in "on-treatment patients" with a minimum number of claims during the follow-up period (at least 5 claims for a 6-month follow-up and at least 10 claims for a 12-month follow-up) to ensure sufficient treatment exposure

- ≥6 months of pre-index continuous enrollment in PharMetrics® Plus
- ≥ 6 months of post-index continuous enrollment in PharMetrics Plus.

  Outcomes will also be assessed at 12 months post-index in a subset of patients with ≥12 months of continuous enrollment after the index date in patients with sufficient follow-up and sample

- Patients with ≥ 2 exacerbations in the 12-month pre index period

- **Follow-up**

  Patients will be followed over a fixed 6-month follow-up period. The follow-up period will end on the last date of continuous enrollment.

  Outcomes will also be assessed by comparing the 12 months pre-index and 12 months post-index in the subgroup of patients with ≥12 months of continuous post-index enrollment (sample permitting).

- **Variables**
  - Primary Outcome Variable(s)
    - among subsets of on-treatment patients without evidence of use of other asthma biologics during the pre-index period and with sufficient follow-up
      - AAER (events per patient-year) in the pre-index and post-index period
      - AAER reduction between the 6 month pre- and 6-month post-index periods (reported as percentage [%] reduction and as an absolute AAER difference)
      - AAER reduction between the 12 month pre- and 12-month post-index periods (reported as percentage [%] reduction and as an absolute AAER difference) (sample permitting)

    Asthma exacerbations will be defined as ≥1 of the following. No more than one exacerbation within any 14-day period will be counted as a separate, new exacerbation.

    - Inpatient admission with a primary discharge diagnosis of asthma
    - ≥1 ED or urgent care visit claim carrying an asthma diagnosis code in any position and receipt of systemic corticosteroids within 7 days (1 dose of injectable steroids or OCS for ≥3 days).
    - ≥1 outpatient visit (not including ED or urgent care) claim carrying an asthma diagnosis code in any position and receipt of systemic corticosteroids within 7 days (1 dose of injectable steroids or OCS for ≥3 days).

– Exploratory outcome(s)

CCI

- **Study Sample Size**

  Sample sizes were estimated assuming 85% power, a mean difference in annual number of exacerbations ranging from 1.0 to 2.0 and correlation between pre- and post-index rates ranging from 0.2 to 0.8. Sample size estimates needed to detect a difference range from 20 to 289 patients. Specifically, assuming a baseline AAER of 2.7 and a reduction of 74% based on the before and after Tezspire analysis of the pooled NAVIGATOR and PATHWAY data (i.e., an absolute AAER reduction of 2.0), the sample required for the primary outcome would by 74 patients assuming a 0.2 correlation.

- **Data Analysis**

  Categorical study variables will be reported as frequencies (counts and percentages). Continuous variables will be described by means, standard deviation (SD), median, and ranges. Asthma exacerbations will be reported as AAER (events per patient-year) assessed during the pre- and post-index, separately. One-sided paired t-tests will be used to test for differences in continuous outcomes observed between the pre- and post-index. McNemar-Bowker tests will be used to assess for pre-post differences in categorical variables.

CCI