NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Real-world comparative effectiveness of tofacitinib, tumour necrosis factor inhibitors, and interleukin 17 inhibitors among patients with axial spondylarthritis and psoriatic arthritis.
Protocol number	A3921446
Protocol version identifier	Version 1.0
Date	23 August 2024
EU Post Authorization Study (PAS) register number	EUPAS1000000226
Active substance	L04AA29 – Tofacitinib citrate
Medicinal product	Xeljanz® (Tofacitinib)
Research question and objectives	*Research questions:* How does real-world treatment effectiveness compare among AxSpA and b/tsDMARD-naive PsA patients treated with tofacitinib, TNFi, and IL-17i? How do the rates of drug persistence for AxSpA and b/tsDMARD-naive PsA patients compare when treated with tofacitinib, TNFi, and IL-17i? How do the healthcare resource utilization patterns and associated costs for AxSpA patients compare when treated with tofacitinib, TNFi, and IL-17i? *Primary objective:* Objective 1.1: To compare the proportion of AxSpA patients fulfilling effectiveness criteria within 6 months after initiating treatment with tofacitinib vs TNFi vs IL-17i –

	among patients with at least 6 months of continuous enrollment after index date. Objective 1.2: To compare the proportion of b/tsDMARD-naive PsA patients fulfilling effectiveness criteria within 6 months after treatment with tofacitinib vs TNFi vs IL-17i – among patients with at least 6 months of continuous enrollment after index date. *Secondary objectives:* Objective 2.1: To compare the proportion of AxSpA patients fulfilling effectiveness criteria within 12 months after initiating treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date. Objective 2.2: To compare the proportion of b/tsDMARD-naive PsA patients fulfilling effectiveness criteria within 12 months after initiating treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date. Objective 2.3: Evaluate drug persistence (median time to therapy discontinuation) among AxSpA patients within 12 months of treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date. Objective 2.4: Evaluate drug persistence (median time to therapy discontinuation) among b/tsDMARD-naive PsA patients within 12 months of treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date. Objective 2.5: Evaluate health care resource utilization and costs for AxSpA patients

	within 6 and 12 months of treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 6 months or 12 months of continuous enrollment after index date, respectively.
Country(ies) of study	United States
Author	Redacted [redacted]

1. TABLE OF CONTENTS

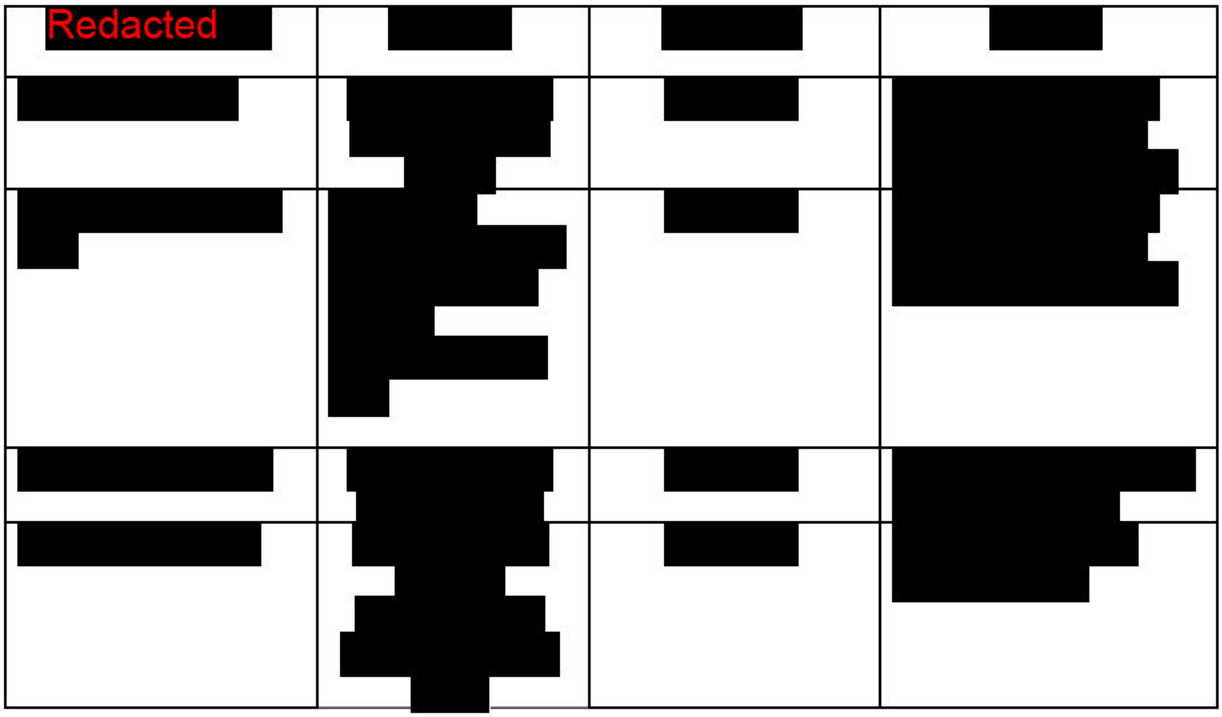
2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AS	Ankylosing spondylitis
AxSpA	Axial spondyloarthritis
bDMARD	Biological disease-modifying anti-rheumatic drug
CI	Confidence interval
CPT-4	Current Procedural Terminology, Fourth Edition
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
GC	Glucocorticoid
GEE	Generalized Estimating Equations
GLM	Generalized linear model
HCPCS	Healthcare Common Procedure Coding System
HCRU	Healthcare resource units
HR	Hazard ratio
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IL-17i	Interleukin-17 inhibitor
IPTW	Inverse Probability of Treatment Weighting
JAKi	Janus kinase inhibitors
KM	Kaplan-Meier
NSAID	Non-steroidal anti-inflammatory drug
PDC	Proportion of days covered

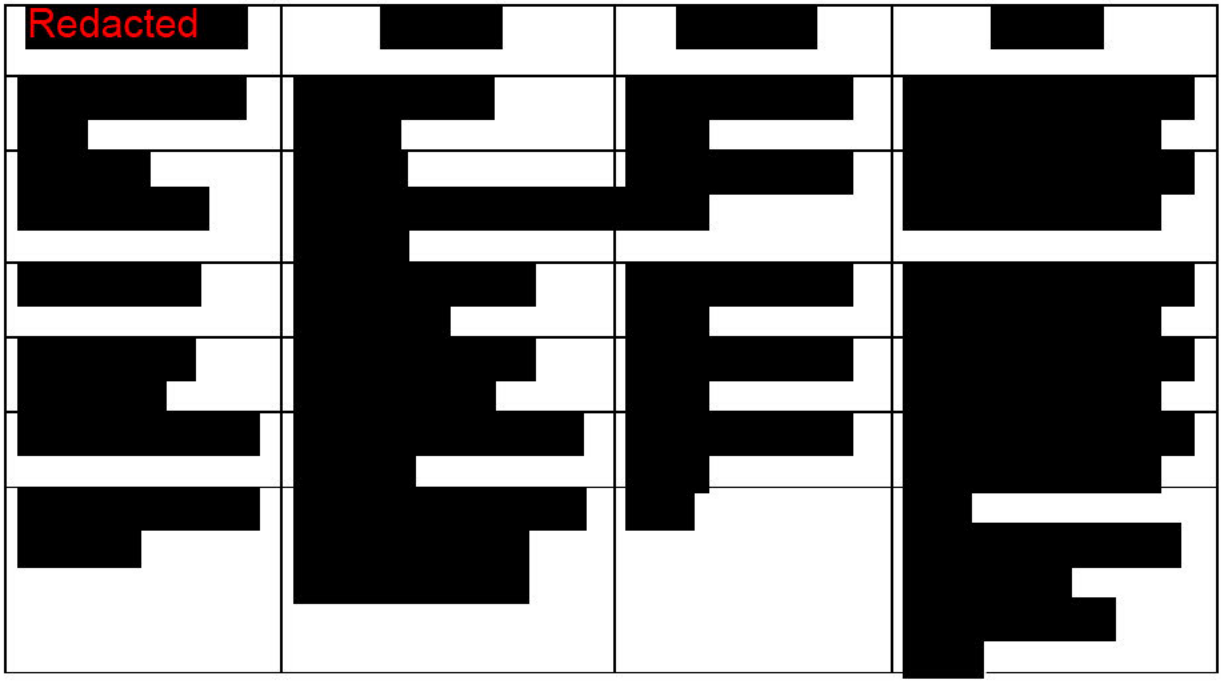
PDE4i	Phosphodiesterase -4 inhibitors
PS	Propensity score
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RWD	Real world data
TNFi	Tumor necrosis factor inhibitor
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drug
UC	Ulcerative colitis
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol



External Collaborators



4. ABSTRACT

- **Title, with subtitles including version and date of the protocol and name and affiliation of main author**

  Title: Real-world comparative effectiveness of tofacitinib, tumour necrosis factor inhibitors, and interleukin 17 inhibitors among patients with axial spondylarthritis and psoriatic arthritis
  Version 1.0 (23 August 2024)
  Redacted

- **Rationale and background**

In the context of the expanding therapeutic landscape and absence of large-scale head-to-head randomized clinical trials, clinical data on direct comparison of efficacy between therapies are lacking in PsA and AxSpA. While certain clinical studies establishing the efficacy and safety of treatments have included internal controls (ie, adalimumab control in OPAL Broaden), these were not powered as formal direct comparisons and this information remains essential for informed clinical-decision making.[18] In the literature, systematic reviews and meta-analyses have compiled the randomized controlled trials of these products to compare their efficacy with that of TNFi.[19,20] While clinical trials provide valuable insights, real-world studies are essential to assess the effectiveness of drugs in everyday clinical practice. A recent study by Zhang et al (2021) assessed the comparative effectiveness of IL-12/23i, IL-17Ai, PDE4i and TNFi for PsA using a claims-based algorithm within an administrative database.[21] Tofacitinib comparative effectiveness has not been studied using this algorithm that originally characterized effectiveness of treatments for RA.[22] This algorithm has also been modified for use in AS.[23]

- This non-interventional study aims to provide data on the comparative real-world clinical effectiveness of advanced therapies (tofacitinib, TNFi, and IL-17i) as well as their associated costs and resource utilization using an adapted version of the claims-based algorithm within a US administrative database in patients with AxSpA and PsA. The results are intended to provide useful information to healthcare professionals and patients in clinical decision making for patients with these conditions.

- **Research question and objectives**

  Research questions addressed by this study using retrospective healthcare claims data from a large US claims database are as follows:

  1. How does real-world treatment effectiveness compare among AxSpA and b/tsDMARD-naive PsA patients treated with tofacitinib, TNFi, and IL-17i?

  2. How do the rates of drug persistence for AxSpA and b/tsDMARD-naive PsA patients compare when treated with tofacitinib, TNFi, and IL-17i?

  3. How do the healthcare resource utilization patterns and associated costs for AxSpA patients compare when treated with tofacitinib, TNFi, and IL-17i?

- **Objectives:**

The primary objectives for this study are:

Objective 1.1: To compare the proportion of AxSpA patients fulfilling effectiveness criteria within 6 months after initiating treatment with tofacitinib vs TNFi vs IL-17i among patients with at least 6 months of continuous enrollment after index date.

Objective 1.2: To compare the proportion of b/tsDMARD-naive PsA patients fulfilling effectiveness criteria within 6 months after initiating treatment with tofacitinib vs TNFi vs IL-17i –among patients with at least 6 months of continuous enrollment after index date.

The secondary objectives for this study are:

Objective 2.1: To compare the proportion of AxSpA patients fulfilling effectiveness criteria within 12 months after initiating treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date.

Objective 2.2: To compare the proportion of b/tsDMARD-naive PsA patients fulfilling effectiveness criteria within 12 months after initiating treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date.

Objective 2.3: Evaluate drug persistence (median time to therapy discontinuation) among AxSpA patients within 12 months of treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date.

Objective 2.4: Evaluate drug persistence (median time to therapy discontinuation) among b/tsDMARD-naive PsA patients within 12 months of treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date.

Objective 2.5: Evaluate health care resource utilization and costs for AxSpA patients within 6 and 12 months of treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 6 months and 12 months of continuous enrollment after index date, respectively.

- **Study design**
  - This non-interventional study is a population-based retrospective cohort study of adults (ages ≥18 years of age) with AxSpA and PsA identified through a large US administrative claims database. The analyses will be conducted separately for the AxSpA and PsA samples.
  - De-identified individual patients who initiated one of the study advanced treatments will be selected from the Komodo's Healthcare database between 14 December 2021, and most recent data available for the AxSpA sample and 14 December 2017, and most recent data available for the PsA sample (start of the identification period is based on FDA approval dates for tofacitinib).
  - The index date will be defined as the date of initiation (first time use) of one of the selected treatments (ie, tofacitinib, TNFi or IL-17i) within the specified identification period for each sample. First time use will be defined as a prescription fill/administration for a drug for which we are not observing any prescription fill/administration at any time prior to the index date, using all available data. For the AxSpA sample, patients may contribute to multiple time segments/index date of the study if they switch to another advanced treatment (first time use) over the index identification period. Patients will be required to have at least 12 months of continuous enrollment (medical and pharmacy benefits) prior to the index date and at least 6 months after the index date. Analysis will be replicated for a subset of patients with at least 12 months of continuous enrollment after the index date.
  - The baseline period will be defined as the 12 months before index date but all historical data available will be used to identify use of prior conventional DMARDs, biologic DMARD, and tsDMARD. Patient's demographic and clinical characteristics will be characterized at index date or during the baseline period, depending on the study variable. History of comorbid conditions will also be assessed by looking at all historical data available for the patient. Treatment effectiveness and healthcare resource utilization and costs will be assessed over the 6 and 12 months following the index date. Persistence on the index treatment will be assessed over the 12 months following the index date.
- **Population**
  - Setting:

- This study will use a retrospective observational study design. The cohort of eligible study patients will be identified from the Komodo Healthcare Map database (Komodo).

- Inclusion Criteria:

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Aged ≥18 years at index date.

2. Evidence of at least one inpatient or at least 2 outpatient claims with a diagnosis code for AxSpA (AxSpA sample) or PsA (PsA sample) >30 days apart over the entire period covered by the data (see ICD-10 codes list in Annex 1).

3. Evidence of initiation (first time use) for at least 1 approved advanced treatment as defined in Section 9.1 during the identification period

    a. The index date will be defined as the date of initiation of a new advanced treatment (first time use) – index date identified over the index identification period (see Figure 1 and Figure 3).

        i. The initiation of a new treatment (first time use) will be defined as a prescription fill/administration for a drug for which we are not observing any prescription fill/administration at any time prior to the index date, using all available data.

    b. For the AxSpA sample, patients may contribute to multiple time segments to the study if they switch to another selected advanced medication (first time use) over the index identification period (ie, a patient could have multiple index date).

4. At least one diagnosis for AxSpA (AxSpA sample) or PsA (PsA sample) on or during the 12 months before index date.

5. At least 12 months of continuous medical enrollment (medical and pharmacy coverage) prior to index date (allowing for enrollment gaps of 30 days or less).

6. At least 6 months of continuous enrollment in database after index date (medical and pharmacy coverage and allowing for enrollment gaps of 30 days or less).

    a. Analysis will be replicated for the subset of patients with at least 12 months of continuous enrollment after index date.

Exclusion Criteria:

Patients meeting any of the following criteria will not be included in the study:

- Combination therapy, with more than 1 advanced therapy prescribed simultaneously on index date (ie, more than one advanced therapy administered on the index date or more than one advanced therapy with a prescription fill on the index date).

Additional Exclusion Criteria for the b/tsDMARD-Naive PsA Cohort

1. Patients with ≥1 claim for any of the treatments below any time prior to the index date:

   a. Includes JAKi (tofacitinib, upadacitinib), PDE4 inhibitor (apremilast), IL-12/-23i (ustekinumab), TNFi (adalimumab, golimumab, infliximab, etanercept, certolizumab), IL-17i (ixekizumab, secukinumab, brodalumab, bimekizumab), IL-23i (risankizumab or guselkumab), CTLA-4i (abatacept), TYK2 (deucravacitinib)

- **Variables – include exposures, outcomes, and key co-variates**

  - The primary outcome of this study is the effectiveness of the index medications (tofacitinib, and TNFi and IL-17i) among patients with AxSpA and b/tsDMARD-naive PsA at 6 months.

  - Effectiveness Criterion:

    1. High adherence (PDC ≥80%)

    2. No switching/adding another non-index advanced therapy

    3. No dose escalation or increased frequency of the index advanced therapy

    4. No addition of new csDMARD not already taken during baseline period or at index

    5. No increase in dose of oral glucocorticoid compared with baseline

    6. No more than a single intraarticular joint injection on more than one unique calendar day between index date +90 days and index date +365 days, inclusive.

    7. No use of pain medication class not observed during baseline period or at index

    8. No use of new topical treatment, actinotherapy or oral retinoid not observed during baseline period or at index **(PsA only)**

    9. No use of spinal procedure for axSpA **(AxSpA only)**

  - Secondary Outcomes include persistence, healthcare resource utilization and costs

- Variables Include:

- Advanced treatment, time since prior advanced treatment, steroid during baseline and 14 days prior to index, Use of csDMARDs during baseline and concomitant use, Use of NSAIDs during baseline and concomitant use, Use of topical treatments during baseline and concomitant use, Use of opioids during baseline and concomitant use, Use of other pain medications during baseline and concomitant use, duration of continuous enrollment before index, age, sex, year of index, insurance type, US geographic region, baseline comorbidities, baseline Charlson Comorbidity index

- **Data sources**

  - The Komodo database is a large US administrative claims database which includes longitudinal information on patients' demographics, medical history, medication use, and healthcare utilization and costs. The claims data is mainly sourced from commercial, Medicaid and Medicare Advantage health plans covering more than 330 million lives over time across the United States. In the Komodo's Healthcare Map database, diagnoses, procedures, and prescription drugs are coded using the International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9/10-CM), the Current Procedural Terminology, Fourth Edition (CPT-4), Healthcare Common Procedure Coding System (HCPCS) codes and National Drug Code (NDC).

- **Study size**

  - PsA b/tsDMARD Naive Cohort:

  - Preliminary feasibility analysis indicates a sample size range of approximately 600 patients on tofacitinib who are bDMARD naive, approximately 30,000 patients on TNFi and approximately 10,000 patients on Il-17i with continuous health care plan enrollment at least 365 days after index date.

  - AxSpA Cohort:

  - Preliminary feasibility analysis indicates a sample size of at least 500 patients on tofacitinib, approximately 8,000 patients on TNFi and approximately 2,000 patients on Il-17i with continuous health care plan enrollment at least 180 days after index date.

- **Data analysis**

Detailed methodology for summary and statistical analyses of data in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major

modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

All analyses will be done separately by indication.

Propensity-score (PS) methods will be employed. PS will be estimated for index medication class (ie, tofacitinib, TNFi, IL-17i) for each patient's exposure - allowing for multiple exposures (multiple index dates/medications) per patient over the study period for the AxSpA sample. Only patients in the AxSpA sample will be allowed to have multiple index dates/index medications as the analyses for PsA will be limited to the subset of b/tsDMARD-naïve patients. Variables to be assessed for inclusion in the PS estimation model will follow those listed in Table 1, Table 2 and Table 3 (depending upon indication), especially those noted as "Baseline characteristics and potential confounder". Other independent variables may also be assessed. For patients in the AxSpA sample, baseline characteristics will be assessed at the time of each treatment initiation (each index date).

Weighted (ie, inverse probability of treatment weighting, IPTW) time-to-event analyses (eg, Cox proportional hazards) will compare failure of the effectiveness criteria, for the index medication classes (TNFi or IL-17i) versus tofacitinib. Estimates (eg, hazard ratios) with 95% CIs will be provided.

Weighted (IPTW) generalized linear models (GLM) (or two-part model) with for instance Generalized Estimating Equations (GEE) for correlated data (for the AxSpA sample) will be applied for continuous measures (eg, Poisson distribution for count measures and gamma distribution for costs).

Analyses will also be conducted using a longer period of 12 months (365 days) after index date for describing the effectiveness criteria amongst the 3 groups to evaluate changes within a longer period of time.

In addition, the following sensitivity analyses, using a modified claims-based algorithm will be performed:

a. Excluding criterion 1 (high adherence) to avoid bias estimating adherence of drugs with different administration routes using health claims data.

b. Exclude criterion 3 (no increase in dose or frequency of index drug), because patients starting therapy with tofacitinib, and some biologics usually do not change the initial dose and/or the frequency.

c. Criteria 5 will be updated to use a cutoff of 50% (instead of 20%) to identify increase in dose of oral glucocorticoid.

d. Exclude criterion 5 due to shorter time for outcome measure for the analyses at 6 months

e. Criteria 3: For patients who only receive IV administrations, upon sufficient sample size, a sensitivity analysis, assessing dose escalation based on both the frequency of administration and dosage change may be considered for the subset of patients with available dosage information.

Depending on the extent of missing data, multiple imputation methods may be undertaken. Missing data methods are fully described in the SAP.

Secondary outcomes of drug persistence, HCRU and cost will be further defined and elaborated from an analysis perspective within the SAP.

- **Milestones**

Milestone	Planned Date
Completion of feasibility assessment	20 May 2024
Start of data collection	29 October 2024
End of data collection	30 April 2025
Registration in the HMA-EMA Catalogues of RWD studies	28 October 2024
Final study report	30 November 2025

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Completion of feasibility assessment	20 May 2024
Start of data collection	29 October 2024
End of data collection	30 April 2025
Registration in the HMA-EMA Catalogues of RWD studies	28 October 2024
Final study report	30 November 2025

7. RATIONALE AND BACKGROUND

Ankylosing spondylitis (AS), also known as radiographic axial spondyloarthritis (AxSpA), and psoriatic arthritis (PsA) are immune-mediated diseases characterized by chronic inflammation in the musculoskeletal system with multi-domain and often extra-articular manifestations.[1,2] AS and PsA prevalence in the United States (US) has been estimated between 0.2%-1% and 0.05%- 0.25%, respectively.[3-5] AS primarily affects the axial skeleton and sacroiliac joints, leading to progressive stiffness and impaired mobility. PsA, a seronegative spondylarthritis, not only affects the joints but also shows skin manifestations and can be present in up to 30% of psoriasis patients.[1,2,6] Managing these conditions involves mitigating symptoms, slowing disease progression, and improving patients' quality of life. Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) have been used as first-line therapies for the management of AS and PsA, respectively.[8,9]

Patients with inadequate response to conventional therapies are treated with advanced therapies, which include inhibitors of phosphodiesterase 4, tumor necrosis factor inhibitors (TNFi), inhibitors of interleukin (IL)-17 and -23 (IL-17i and IL-23i), and Janus kinase inhibitors (JAKi).[10-14]

JAKi are small molecule drugs with rapid onset of action, oral administration, short half-life, and lack of immunogenicity compared to biologics. Tofacitinib is a JAKi that preferentially inhibits signaling by cytokine receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. It is approved for 5 indications in the US: adults with moderately to severely active rheumatoid arthritis (RA), adults with active psoriatic arthritis (PsA), adults with moderately to severe ulcerative colitis (UC), adults with active ankylosing spondylitis (AS), and patients 2 years of age or older with polyarticular course juvenile idiopathic arthritis (JIA).[15] Tofacitinib received approval by the FDA for PsA on 14 December 2017 and for AS on 14 December 2021.[16,17]

In the context of the expanding therapeutic landscape and absence of large-scale head-to-head randomized clinical trials, clinical data on direct comparison of efficacy between therapies are lacking. While certain clinical studies establishing the efficacy and safety of treatments have included internal controls (ie, adalimumab control in OPAL Broaden), these were not powered as formal direct comparisons and this information remains essential for informed clinical-decision making.[18] In the literature, systematic reviews and meta-analyses have compiled the randomized controlled trials of these products to compare their efficacy with that of TNFi.[19,20] While clinical trials provide valuable insights, real-world studies are essential to assess the effectiveness of drugs in everyday clinical practice. A recent study by Zhang et al (2021) assessed the comparative effectiveness of IL-12/23i, IL-17Ai, PDE4i and TNFi for PsA using a claims-based algorithm within an administrative database.[21] Tofacitinib comparative effectiveness has not been studied using this algorithm that originally characterized effectiveness of treatments for RA.[22] This algorithm has also been modified for use in AS.[23]

This non-interventional study aims to provide data on the comparative real-world clinical effectiveness of advanced therapies (tofacitinib, TNFi, and IL-17i) as well as their associated costs and resource utilization using an adapted version of the claims-based algorithm within a US administrative database in patients with AxSpA and PsA. The results are intended to provide useful information to healthcare professionals and patients in clinical decision making for patients with these conditions.

This noninterventional study is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Questions

Research questions addressed by this study using retrospective healthcare claims data from a large US claims database are as follows:

1. How does real-world treatment effectiveness compare among AxSpA and b/tsDMARD-naive PsA patients treated with tofacitinib, TNFi, and IL-17i?

2. How do the rates of drug persistence for AxSpA and b/tsDMARD-naive PsA patients compare when treated with tofacitinib, TNFi, and IL-17i?

3. How do the healthcare resource utilization patterns and associated costs for AxSpA patients compare when treated with tofacitinib, TNFi, and IL-17i?

8.2. Study Objectives:

8.2.1. Primary Objective

The primary objectives for this study are:

Objective 1.1: To compare the proportion of AxSpA patients fulfilling effectiveness criteria within 6 months after initiating treatment with tofacitinib vs TNFi, vs IL-17i – among patients with at least 6 months of continuous enrollment after index date.

Objective 1.2: To compare the proportion of b/tsDMARD-naive PsA patients fulfilling effectiveness criteria within 6 months after initiating treatment with tofacitinib vs TNFi vs IL-17i – among patients with at least 6 months of continuous enrollment after index date.

8.2.2. Secondary Objectives

The secondary objectives for this study are:

Objective 2.1: To compare the proportion of AxSpA patients fulfilling effectiveness criteria within 12 months after initiating treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date.

Objective 2.2: To compare the proportion of b/tsDMARD-naïve PsA patients fulfilling effectiveness criteria within 12 months after initiating treatment with tofacitinib vs TNFi vs

IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date.

Objective 2.3: Evaluate drug persistence (median time to therapy discontinuation) among AxSpA patients within 12 months of treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date.

Objective 2.4: Evaluate drug persistence (median time to therapy discontinuation) among b/tsDMARD-naive PsA patients within 12 months of treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 12 months of continuous enrollment after index date.

Objective 2.5: Evaluate health care resource utilization and costs for AxSpA patients within 6 and 12 months of treatment with tofacitinib vs TNFi vs IL-17i – among the sample of patients with at least 6 months or 12 months of continuous enrollment after index date, respectively.

9. RESEARCH METHODS

9.1. Study Design

This non-interventional study is a population-based retrospective cohort study of adults (ages ≥18 years of age) with AxSpA or PsA identified through a large US administrative claims database. The analyses will be conducted separately for the AxSpA and PsA samples.

De-identified individual patient who initiated one of the study advanced treatments will be selected from the Komodo's Healthcare database between 14 December 2021, and most recent data available for the AxSpA sample and 14 December 2017, and most recent data available for the PsA sample (start of the identification period is based on FDA approval dates for tofacitinib for AS and PsA).

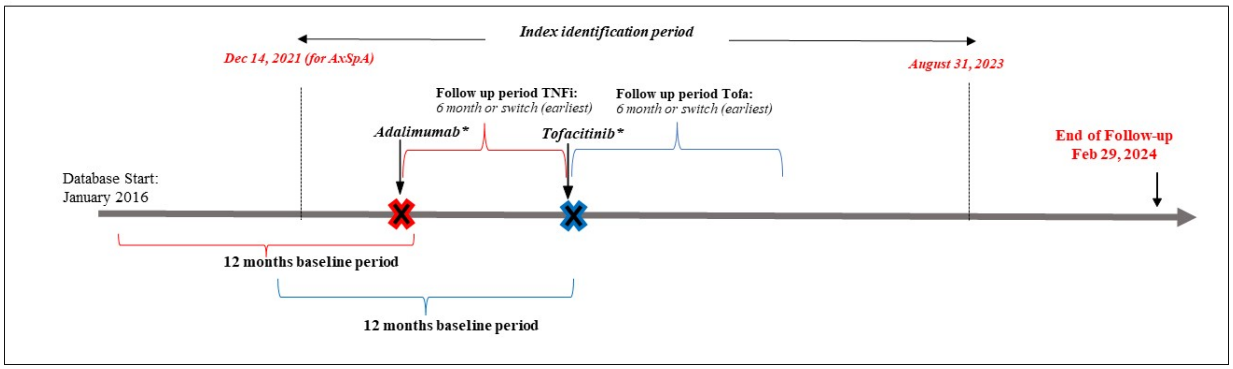
The index date will be defined as the date of initiation (first time use) for one of the selected advanced treatments (ie, tofacitinib, TNFi or IL-17i) within the specified identification period for each sample. First time use will be defined as a prescription fill/administration for a drug for which we are not observing any prescription fill/administration at any time prior to the index date, using all available data. For the AxSpA sample, patients may contribute to multiple time segments/index date of the study if they switch to another advanced treatment over the index identification period.

Patients will be required to have at least 12 months of continuous enrollment (medical and pharmacy benefits) prior to the index date and at least 6 months after the index date. Analysis will be replicated for a subset of patients with at least 12 months of continuous enrollment after the index date.

The baseline period will be defined as the 12 months before index date, but all historical data available will be used to identify use of prior conventional DMARDs, biologic DMARD, and tsDMARD. Patient's demographic and clinical characteristics will be characterized at index

date or during the baseline period, depending on the study variable. History of comorbid conditions will be assessed during the 12 months baseline period as well as looking at all historical data available for the patient. Treatment effectiveness and healthcare resource utilization and costs will be assessed up to 6 and 12 months following the index date. Persistence on the index treatment will be assessed over the 12 months following the index date.

Figure 1a. Study Diagram for AxSpA– 6 Months Follow up Period



**Only initiation of new advanced treatment (first time use) will be considered to be a potential index date. First time use will be defined as a prescription fill/administration for a drug for which we are not observing any prescription fill/administration at any time prior to the index date, using all available data.*

Figure 2b. Study Diagram for PsA b/tsDMARD-naive patients – 6 Months Follow up Period

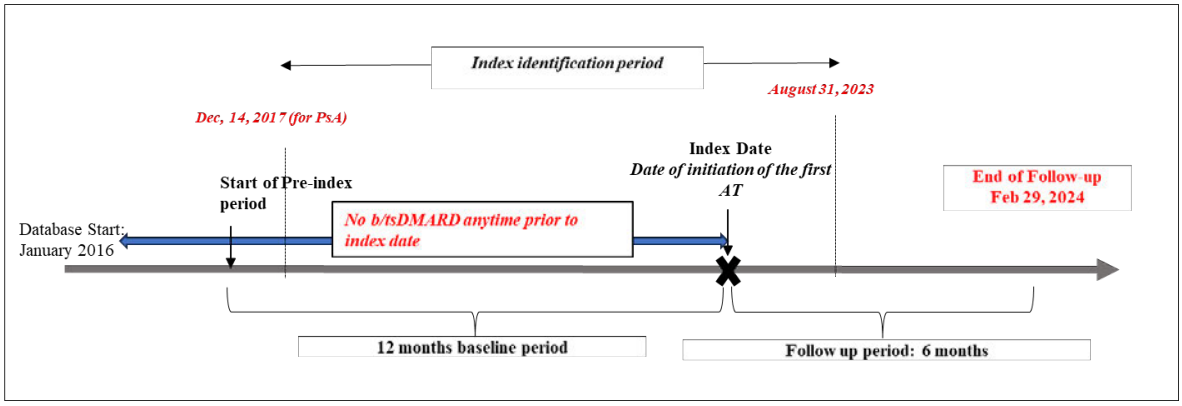
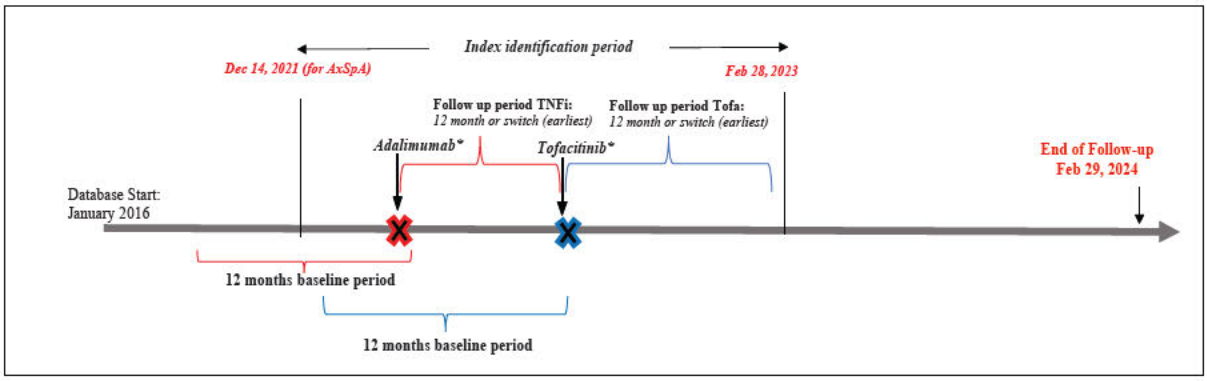
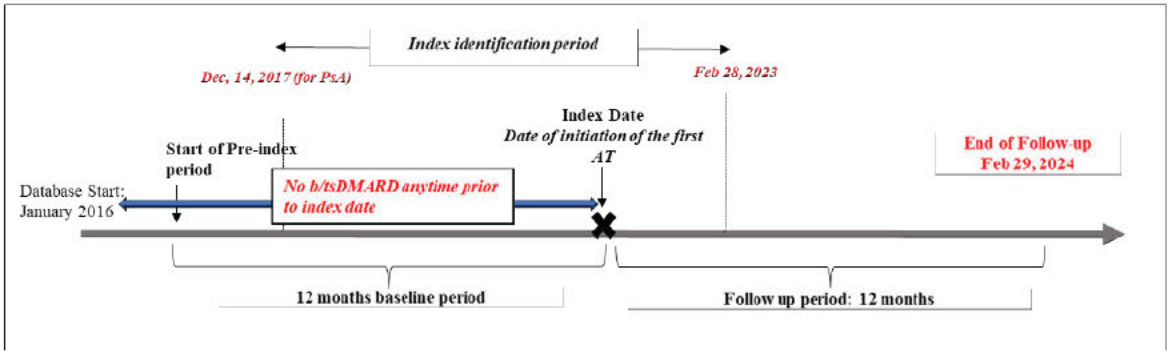


Figure 3a. Study Diagram for AxSpA– 12 Months Follow up Period



**Only initiation of new advanced treatment (first time use) will be considered to be a potential index date. First time use will be defined as a prescription fill/administration for a drug for which we are not observing any prescription fill/administration at any time prior to the index date, using all available data.*

Figure 4b. Study Diagram for PsA b/tsDMARD-naive patients – 12 Months Follow up Period



*AT: Advanced treatment: ie, tofacitinib, TNFi or IL-17i*For illustration purposes, the calendar axis may not be proportional*

9.2. Setting

Komodo is a large US administrative claims database which includes adjudicated longitudinal information on patients' demographics, medical history, medication use, and healthcare utilization and costs (ie, estimated allowed amount). The claims data is mainly from commercial, Medicaid and Medicare Advantage health plans covering more than 300 million lives over time across the United States. Identification of disease populations, outcomes of interest, and drugs prescribed will be implemented using International Classification of Diseases – Tenth Revision (ICD-10) codes, current procedure terminology (CPT) procedure codes, and prescribing data (eg, National Drug Center (NDC) codes) in the patients' records.

After identifying patients with indications of interest, all patients who meet the inclusion and exclusion criteria listed under Section 9.2.1 and will be included. For primary objectives 1.1

and 1.2, as well as secondary objectives 2.1 to 2.5 patients meeting the inclusion and exclusion criteria will be classified under the following exposure categories based on the treatment that was initiated on the index date: (1) tofacitinib; or (2) TNFi (adalimumab, golimumab, infliximab, etanercept, certolizumab pegol) or IL-17i: (ixekizumab, secukinumab).

Baseline period: 12 months prior to the index date. Use of conventional DMARDs, biologic DMARDs and tsDMARD will be assessed by looking at all available data before the index date. History of comorbid conditions will be assessed during the 12 months baseline period as well as looking at all historical data available for the patient.

Follow-up period: patients will be followed from index date (inclusive) up to the earliest of 6 (or 12) months after the index date (depending on the study population and study outcome) or date of switch to another selected advanced medication.

Exposure to therapies will be defined using the NDC for dispensed medications and, where relevant, procedure codes (CPT/HCPCS) for injection or infusion.

For both samples, the initiation of a new treatment (first time use) will be defined as a prescription fill/administration for a drug for which we are not observing any prescription fill/administration at any time prior to the index date, using all available data.

The analyses will be conducted separately for the AxSpA and b/tsDMARD- naïve PsA sample, although study samples may overlap if patients meet inclusion criteria for both samples.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Aged ≥18 years at index date
2. Evidence of at least one inpatient or at least 2 outpatient claims with a diagnosis code for AxSpA (AxSpA sample) or PsA (PsA sample) >30 days apart over the entire period covered by the data (please see ICD-10 codes list in Annex 1).
3. Evidence of initiation (first time use) for at least 1 approved advanced treatment as defined in Section 9.1 during the identification period
    a. The index date will be defined as the date of initiation of a new advanced treatment (first time use) – index date identified over the index identification period (please see Figure 1 and Figure 3)
        i. *The initiation of a new treatment (first time use) will be defined as a prescription fill/administration for a drug for which we are not observing any prescription fill/administration at any time prior to the index date, using all available data*

b. For the AxSpA sample, patients may contribute to multiple time segments of the study if they switch to another advanced medication (first time use) over the index identification period (ie, a patient could have multiple index date).

4. At least one diagnosis for AxSpA (AxSpA sample) or PsA (PsA sample) on or during the 12 months before the index date

5. At least 12 months of continuous medical enrollment (medical and pharmacy coverage) prior to index date (allowing for enrollment gaps of 30 days or less).

6. At least 6 months of continuous enrollment in database after index date (including index date) - medical and pharmacy coverage and allowing for enrollment gaps of 30 days or less.

   a. Analysis will be replicated for the subset of patients with at least 12 months of continuous enrollment after index date (including index date).

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Combination therapy, with more than 1 advanced therapy prescribed simultaneously on index date (ie, more than one advanced therapy administered on the index date or more than one advanced therapy with a prescription fill on the index date).

Additional Exclusion Criteria for the b/tsDMARD-Naive PsA Cohort

1. Patients with ≥1 claim for any of the treatments below any time prior to the index date:

   a. Includes JAKi (tofacitinib, upadacitinib), PDE4 inhibitor (apremilast), IL-12/-23i (ustekinumab), TNFi (adalimumab, golimumab, infliximab, etanercept, certolizumab), IL-17i (ixekizumab, secukinumab, brodalumab, bimekizumab), IL-23i (risankizumab or guselkumab), CTLA-4i (abatacept), TYK2 (deucravacitinib)

9.3. Variables

9.3.1. Baseline Demographics and Clinical Characteristics

Variables utilized in this study include baseline demographics and clinical characteristics, comorbidities, and medications. All variables will be specifically defined in the SAP, including code lists and time periods of interest where applicable.

Table 1. General Variables Evaluated and Analyzed in this Study for AxSpA and b/tsDMARD-naive PsA Cohorts

Variable	Role	Data Source(s)	Operational definition
Selected advanced treatment for cohort creation	Exposure (treatment variable)	Komodo	Either tofacitinib or a TNFi: adalimumab, golimumab, infliximab, etanercept, certolizumab or a IL-17i: ixekizumab, secukinumab
Time since prior advanced	Baseline characteristic	Komodo	Among those who used at least one advanced medication prior to index, time between last days

Variable	Role	Data Source(s)	Operational definition
treatment	and potential confounder		of supply/administration for the last prescription for a b/tsDMARD before index date and index date.
Use of steroids during the baseline period	Baseline characteristics and potential confounder	Komodo	Number and proportion of patients who use steroids during the 365 days baseline period will be reported overall as well as separately for each route of administration as described below. Duration and dose will also be characterized. • Patients with steroid usage, N (%) o Oral, N (%) ▪ Cumulative dosage expressed in prednisolone-equivalent dose , continuous (mean, SD, median, Q1, Q3, min, max) ▪ Average duration in days, continuous (mean, SD, median, Q1, Q3, min, max) o Injectable, N (%) ▪ Frequency (mean, SD, median, Q1, Q3, min, max) o Infusion, N(%) ▪ Frequency (mean, SD, median, Q1, Q3, min, max) o Topical, N (%) o Other route of administration, N (%)
Steroid use within 14 days prior to index date	Baseline characteristic	Komodo	Patients with steroids drug on hand (considering days of supply) within 14 days of index date will be reported overall as well as separately for each route of administration as described below. Binary: yes/no. • Patients with steroid usage, N (%) o Oral, N (%) o Injectable, N (%) o Infusion, N (%) o Topical, N (%) o Other route of administration, N (%)
Use of csDMARD during the baseline period	Baseline characteristics	Komodo	Patients with a prescription fill/administration of csDMARD within the 365 days baseline period. Use of csDMARDs will also be assessed looking at all historical data available for the patient. Binary: yes/no Presence of the following will also be described:

Variable	Role	Data Source(s)	Operational definition
			• Methotrexate (oral or sc) • Sulphasalazine/sulfasalazine • Chloroquine • Hydroxychloroquine • Leflunomide
Use of NSAIDs during the baseline period	Baseline characteristics	Komodo	Patients with a prescription fill/administration of NSAID within 365 days baseline period. Binary: yes/no
Use of selected topical treatments and related medical procedures during the baseline period	Baseline characteristics	Komodo	Patients with a prescription fill/administration for selected topical treatments within 365 days baseline period. Binary: yes/no Presence of the following will also be described: • Calcineurin inhibitors • Corticosteroids • Vitamin D analogues • Retinoids • Phototherapy

Use of opioids during the baseline period	Baseline characteristics	Komodo	Patients with a prescription fill/administration of opioid within 365 days baseline period.
			Binary: yes/no
			• Oral, N (%)
			  ○ Average duration in days, continuous (mean, SD, median, Q1, Q3, min, max)
			• Injectable, N (%)
			  ○ Frequency (mean, SD, median, Q1, Q3, min, max).
			• Infusion, N (%)
			  ○ Frequency (mean, SD, median, Q1, Q3, min, max)
			• Transdermal
			  ○ Frequency (mean, SD, median,

Variable	Role	Data Source(s)	Operational definition
			Q1, Q3, min, max) • Topical, N (%) o Frequency (mean, SD, median, Q1, Q3, min, max) Use of strong vs not strong opioid may potentially be described based on data availability
Use of other selected non-opioid pain medication during the baseline period	Baseline characteristics	Komodo	Patients with a prescription fill/administration for selected pain medication within 365 days baseline period. Binary: yes/no The following will also be described at the drug class and medication level; o non-narcotic analgesics (acetaminophen, aspirin) o anticonvulsants o antidepressants o topical pain medications
Concomitant use of csDMARD with index medication during the baseline period	Baseline characteristic	Komodo	Patients with a prescription fill/administration of csDMARD on or within 30 days after the index date. Binary: yes/no Presence of the following will also be described: • Methotrexate (oral or sc) • Sulphasalazine/sulfasalazine • Chloroquine • Hydroxychloroquine • Leflunomide
Concomitant use of NSAIDs with index medication	Baseline characteristics	Komodo	Patients with a prescription fill/administration of NSAID on or within 30 days after the index date. Binary: yes/no
Recent use of NSAIDs	Baseline characteristics	Komodo	Patients with a prescription fill/administration of NSAID within 30 days before index date. Binary: yes/no
Concomitant use of selected topical treatments with index	Baseline characteristics	Komodo	Patients with a prescription fill/administration of selected topical treatments on or within 30 days after the index date. Binary: yes/no Presence of the following will also be described:

Variable	Role	Data Source(s)	Operational definition
medication			• Calcineurin inhibitors • Corticosteroids • Vitamin D analogues • Retinoids • Phototherapy
Recent use of selected topical treatments	Baseline characteristics	Komodo	Patients with a prescription fill/administration of selected topical treatments within 30 days before the index date. Binary: yes/no Presence of the following will also be described: • Calcineurin inhibitors • Corticosteroids • Vitamin D analogues • Retinoids • Phototherapy
Concomitant use of opioids with index medication	Baseline characteristics	Komodo	Patients with a prescription fill/administration of opioid on or within 30 days after the index date. Binary: yes/no The following will also be described: • Oral, N (%) • Injectable, N (%) • Infusion, N (%) • Transdermal, N (%) • Topical, N (%)
Recent use of opioids	Baseline characteristics	Komodo	Patients with a prescription fill/administration of opioid within 30 days before the index date. Binary: yes/no The following will also be described: • Oral, N (%) • Injectable, N (%) • Infusion, N (%) • Transdermal, N (%)

Variable	Role	Data Source(s)	Operational definition
			• Topical, N (%)
Concomitant use of other non-opioid pain medication with index medication	Baseline characteristics	Komodo	Patients with a prescription fill/administration for other pain medications on or within 30 days after the index date. Binary: yes/no, at the drug class and medication level • non-narcotic analgesics • anticonvulsants • antidepressants topical pain medications
Recent use of other non-opioid pain medication	Baseline characteristics	Komodo	Patients with a prescription fill/administration for other pain medications within 30 days before the index date. Binary: yes/no, at the drug class and medication level • non-narcotic analgesics • anticonvulsants • antidepressants • topical pain medications
Duration of continuous enrollment before index date	Baseline characteristic	Komodo	Time between start of continuous enrollment and index date, in days
Age at index	Baseline characteristics and potential confounder	Komodo	Age will be defined as of the index date, mean, median, min and max and with 3 age groups defined: 18-44, 45-65, 65+
Sex	Baseline characteristics and potential confounder	Komodo	Sex will be defined as either male or female as of the index date
Year of index date	Baseline characteristics and potential confounder	Komodo	Year of index date
Insurance type	Baseline characteristics and potential confounder	Komodo	Patient's insurance type as of the index date eg, Commercial, Medicare and Other
US geographic region	Baseline characteristics and potential	Komodo	The US will be divided into five regions: Northeast, South, Midwest, West and unknown.

Variable	Role	Data Source(s)	Operational definition
	confounder		
Baseline Charlson Comorbidity Index (CCI)	Baseline characteristic and potential confounder	Komodo	The Quan- CCI will be assessed during the 365 days before index date. CCI will be reported as a continuous variable, ie, including min, max, mean, median, and for the following categorical variables: 0, 1-2, 3-4 and 5+ Each of the CCI component will also be reported separately ie, • Myocardial infarction (MI) • Congestive heart failure (CHF) • Peripheral vascular disease (PVD) • Cerebrovascular disease (CD) • Dementia • Chronic pulmonary disease (CPD) • Rheumatologic disease (RD) • Peptic ulcer disease (PUD) • Mild liver disease (MLD) • Diabetes without chronic complication • Diabetes with chronic complications • Hemiplegia or paraplegia • Renal disease • Any malignancy, including leukemia and lymphoma • Moderate or severe liver disease • Metastatic solid tumor • AIDS/HIV
Baseline comorbidities	Baseline characteristic and	Komodo	Baseline comorbidities will be assessed during 365 days before index date based on the presence of at least one medical claims with a diagnosis

Variable	Role	Data Source(s)	Operational definition

	potential confounder		code for the selected conditions. History of comorbid conditions will also be assessed looking at all historical data available for the patient.
			
			Presence of each factor will be reported separately (ie, not all grouped into one variable) and include:
			• Hypertension
			• Metabolic syndrome
			• Obesity
			• Hyperlipidemia
			• Any cardiovascular disease
			• Any pulmonary disease (including COPD, asthma, interstitial lung disease)
			• Diabetes
			• Mood/mental disorders (ie, attention hyperactivity deficit disorder, anxiety, depression, obsessive compulsive disorder, substance abuse/dependance)
			• Anemia
			• Fibromyalgia
			• Psoriasis
			• Psoriatic arthritis (AxSpA sample only)
			• AxSpA (PsA sample only)
			• Inflammatory bowel disease (UC or CD)
			  ○ Crohn's disease (CD)
			  ○ Ulcerative colitis (UC)
			• Serious infection
			• Malignancy
			• Myocardial infarction

Variable	Role	Data Source(s)	Operational definition
			• Stroke • Deep vein thrombosis • Pulmonary embolism • Chronic kidney disease • Osteoarthritis • Osteoporosis • Anterior uveitis • Rheumatoid Arthritis • AIDS/HIV

Table 2. Additional Variables Evaluated and Analyzed in the AxSpA Cohort

Variable	Role	Data Source(s)	Operational definition
Prior use of advanced medications	Baseline characteristics and potential confounder	Komodo	Advanced medications will include: tofacitinib, upadacitinib, apremilast, adalimumab, golimumab, infliximab, etanercept, certolizumab, ixekizumab, secukinumab, deucravacitinib, bimekizumab, brodalumab Use of advanced treatments any time prior to index date; binary (yes/no), number of distinct JAKs (0, 1, 2), number of distinct biologics (0, 1, 2, 3, 4+), number of distinct TNFi (0, 1, 2, 3, 4+), number of distinct non-TNFi (0, 1, 2, 3, 4+), and specific medications

Healthcare resource utilization – specialty visits	Baseline characteristics	Komodo	Specialty visits during the 365 days baseline period will be assessed including: (If not specify, variable reported in the unit – per patient per month)
			• All-cause rheumatology visits
			  ○ Patients with rheumatology visits, N (%)
			  ○ Number of rheumatology visits among all patients
			• AxSpA-related rheumatology visits
			  ○ Patients with rheumatology visits, N (%)
			  ○ Number of rheumatology visits among all patients
			  ○ AxSpA-related visits will be defined as visits associated with a diagnosis

			code for AxSpA. In the event where the specialty is missing or unknown for a visit, the visit will be considered to be a rheumatology visit if we observe a diagnosis code for AxSpA during the visit.
Healthcare resource utilization– all cause and AxSpA-related	Baseline characteristics	Komodo	Healthcare resource utilization during the 365 days baseline period will be assessed. AxSpA related visits will be defined as visits associated with a diagnosis code for AxSpA. These include the followings: (If not specify, variable reported in the unit – per patient per month) • All-cause inpatient admissions o Patients with any inpatient admissions, N (%) o Number of all-cause inpatient admissions among all patients o Length of all-cause inpatient admissions in days • AxSpA-related inpatient admissions o Patients with any AxSpA-related inpatient admissions, N (%) o Number of AxSpA-related inpatient admissions among all patients o Length of AxSpA-related inpatient admissions in days • Number of emergency department (ED) visits o All-cause ED visits ▪ Patients with any ED visits, N (%) ▪ Number of all-cause ED visits among all patients o AxSpA-related ED visits ▪ Patients with AxSpA-related ED visits, N (%) ▪ Number of AxSpA-related ED visits among all patients • Number of outpatient visits (eg, includes physician office visits, walk-in retail health clinic visits, and urgent care facility visits; may provide in breakdown in categories like ambulatory surgical center, hospital outpatient department, etc. if data permit) o All-cause outpatient visits (excludes ED visit) ▪ Patients with all-cause outpatient visits, N (%) ▪ Number of all-cause outpatient visits among all patients o AxSpA-related outpatient visits ▪ Patients with AxSpA-related outpatient visits, N (%)

			▪ Number of AxSpA-related outpatient visits among all patients • Number of prescription fill (pharmacy claims) o All-cause prescription ▪ Patients with all-cause prescription, N (%) ▪ Number of all-cause prescription among all patients o AxSpA-related prescription ▪ Patients with AxSpA-related prescription, N (%) ▪ Number of AxSpA-related prescription (csDMARDs, advanced treatment (ie, b/tsDMARDs), NSAIDs, steroid, opioids; see lists from Table 1 Table 1) among all patients
Costs – all cause and AxSpA-related	Baseline characteristics	Komodo	Cost of healthcare resource utilization during the 365 days baseline period will be assessed based on allowed amounts. AxSpA related costs will be defined as costs associated with a diagnosis code for AxSpA in any position. These include the followings: (If not specify, variable reported in the unit – per patient per month) • All-cause inpatient cost o Cost of all-cause inpatient visits among all patients • All-cause rheumatology visit cost o Cost of all-cause rheumatology visits among all patients • All-cause ED cost o Cost of all-cause ED visits among all patients • All-cause outpatient cost (excludes ED cost; may provide in breakdown in categories like ambulatory surgical center, hospital outpatient department, etc. if data permit) o Cost of all-cause outpatient visits among all patients • All-cause pharmacy cost o Cost of all-cause outpatient prescription of medicine among all patients • All-cause total medical cost o Cost of all-cause HCRU among all patients. It's the sum of inpatient, ED, and outpatient costs • All-cause total cost

			Cost of all-cause HCRU among all patients. It's the sum of inpatient, ED, outpatient, and pharmacy costs
			
			• AxSpA-related inpatient cost
			  ○ Cost of AxSpA-related inpatient visits among all patients
			
			• AxSpA-related ED cost
			  ○ Cost of AxSpA-related ED visits among all patients
			• AxSpA-related outpatient cost (may provide in breakdown in categories like ambulatory surgical center, hospital outpatient department, etc. if data permit)
			  ○ Cost of AxSpA-related outpatient visits among all patients
			• AxSpA-related rheumatologist visit cost
			  ○ Cost of AxSpA-related rheumatologist visits among all patients
			• AxSpA-related treatment administration cost
			  ○ Costs associated with AxSpA treatment administration in a medical setting (csDMARDs, advanced treatment (ie, bDMARDs), NSAIDs, steroid, opioids; see lists from Table 1)
			• AxSpA-related pharmacy cost
			  ○ Cost of AxSpA-related prescription of medicine (csDMARDs, advanced treatment (ie, b/tsDMARDs), NSAIDs, steroid, opioids; see lists from Table 1) among all patients
			• Total cost for AxSpA-related treatment administration and pharmacy cost
			  ○ Sum of AxSpA-related treatment administration cost and AxSpA-related pharmacy cost
			• AxSpA-related total medical cost
			  ○ Cost of AxSpA-related medical HCRU among all patients. It's the sum of s inpatient, ED, and outpatient costs
			• AxSpA-related total cost
			  ○ Cost of AxSpA-related HCRU among all patients. It's the sum

			of s AxSpA-related inpatient, ED, outpatient, and pharmacy costs

Table 3. Additional Variables Evaluated and Analyzed in the b/tsDMARD-naive PsA Cohort

Variable	Role	Data Sources	Operational definition
Concomitant use of apremilast	Baseline characteristics	Komodo	Patients with a prescription fill/administration of apremilast on or within 30 days after the index date. Binary: yes/no
Healthcare resource utilization – specialty visits	Baseline characteristics	Komodo	Specialty visits during the 365 days baseline period will be assessed including: (If not specify, variable reported in the unit – per patient per month) • All-cause total rheumatology and dermatology visits o Patients with either rheumatology or dermatology visits, N (%) o Number of rheumatology and dermatology visits among all patients • All-cause rheumatology visits o Patients with rheumatology visits, N (%) o Number of rheumatology visits among all patients • All-cause dermatology visits o Patients with dermatology visits, N (%) o Number of dermatology visits among all patients In the event where the specialty is missing or unknown for a visit, the visit will be considered to be a rheumatology visit if we observe a diagnosis code for PsA during the visit.

9.3.2. Outcome

The primary outcome of this study is the effectiveness of the index medications (tofacitinib, and TNFi and IL-17i) among patients with AxSpA and b/tsDMARD-naive PsA at 6 months.

Effectiveness definition

A claims-based algorithm will be used to assess treatment effectiveness. This algorithm was originally derived and validated for RA using the Veterans Affairs Medicare and pharmacy claims database against the gold standard for effectiveness was measured at the 1-year visit following the index visit and was defined as Disease Activity Score (DAS)28 =< 3.2 units

low disease activity (LDA) or improvement in DAS 28>1.2 units.[11] The claims algorithm was used as a proxy for the clinical effectiveness of RA medications. An adapted but not validated version of this algorithm will be used for this project[23]

In the original algorithm published, the effectiveness outcome was measured at year 1 using following 6 criteria. If all of these 6 criteria' were fulfilled, then the drug was deemed to be effective:

1. High adherence to index drug (required),
2. Biologic switch or add (prohibited),
3. Addition of a new non- biologic DMARD (prohibited),
4. Increase in biologic dose or frequency (prohibited),
5. More than one glucocorticoid (GC) joint injection/IV (prohibited) beyond 90 days and
6. Increase in dose of oral GC compared to baseline (prohibited)

This algorithm has been adapted for use in other therapeutic disease areas including PsA and AS.[23] Below is the adapted version that we intend to use in our study to evaluate comparative effectiveness. The number and proportion of patients satisfying all criteria at month 6 or month 12 post-index will be assessed and reported for AxSpA and PsA, respectively:

Criteria for AxSpA Cohort:

Criteria	Definition
1. High adherence to index treatment	**Proportion of days covered (PDC)≥80%** PDC will be calculated as the ratio of the total number of days with drug at hand to the length of the time periods under investigation (180 and 365 days). Total number of days with drug on hand will be calculated as follows: 1) For outpatient Rx claims, the days' supply values will be summed across all claims for the index drug. 2) For medical claims, days' supply will be equal to the labelled maintenance frequency (SC = subcutaneous, IV = intravenous): a. Adalimumab: 14 days (SC) b. Certolizumab: 28 days (SC) c. Etanercept: 7 days (SC)

Criteria	Definition
	d. Golimumab: 56 days (IV), 28 days (SC) e. Infliximab: 56 days f. Ixekizumab: 28 days (SC) g. Secukinumab: 28 days (SC) h. Tofacitinib: 1 day (Tab) In both cases, overlapping days' supply across fills will be subtracted from the total (with total Rx overlapping days across all fills being capped at 14 days; no cap for medical claims)
2. No switching/adding another non-index advanced AxSpA therapy	Patients who initiate other non-index advanced therapy medications during follow-up period (180 days and 365 days) Advanced AxSpA therapy will include: tofacitinib, upadacitinib, adalimumab, golimumab, infliximab, etanercept, certolizumab, ixekizumab, secukinumab, deucravacitinib, bimekizumab, brodalumab
3. **No dose escalation or increased frequency of the index maintenance dose for advanced therapy**	Dose escalation will be assessed by comparing the first observed maintenance dose for the index advanced therapy after loading to all doses observed during the remainder of follow-up. If any dose is 20% higher than the index maintenance dose, the patient will be flagged as having escalated their dose. Only the index advanced therapy will be assessed. Dose was calculated as follows: 1. For outpatient Rx claims: Dose = (Strength x Quantity Dispensed (QD))/Days' supply 2. For medical claims: Dose = (Strength based on HCPCS code) x (Billed units) (The total dosing amount will be used without considering the time window between two administrations.) For patients who only receive IV administrations, the number of claims will also be calculated. This frequency must be within 120% of the number expected during 1 year time period based on guidelines.

Criteria	Definition
	For patients who only receive IV administrations, upon sufficient sample size, a sensitivity analysis, assessing dose escalation based on both the frequency of administration and dosage change may be considered for the subset of patients with available dosage information.
4. No addition of new csDMARD for AxSpA not already taken during 6 months before or on index date.	Between the index +30 days and end of study period (180 days and 365 days after the index date), patient cannot initiate therapy with a new conventional DMARD (methotrexate, sulfasalazine, leflunomide or hydroxychloroquine) that they were not already taking during the 6 months prior to the index date or used as a concomitant medication with the index treatment. csDMARDs initiated on or during the first 30 days after the index date will be considered to be used in concomitance with the index advanced treatment and will not be considered to be an addition of a new csDMARD.
5. No increase in dose of oral glucocorticoid compared with baseline.	For patients who received no prescriptions for oral glucocorticoids during the 6 months prior to the index date, cannot have received more than 30 days of oral glucocorticoids between the index date + 90 days and the end of the study period (6 months and 12 months after the index date), inclusive. Analysis at 6 months: For patients who received prescriptions for oral glucocorticoids in the 6 months prior to the index date, the cumulative glucocorticoid dose in the 3 months prior to the end of the study period must be similar (that is, within 120%) to the cumulative dose in the last 3 months prior to the index date. Analysis at 12 months: For patients who received prescriptions for oral glucocorticoids in the 6 months prior to the index date, the cumulative glucocorticoid dose in the 6 months prior to the end of the study period must be similar (that is, within 120%) to the cumulative dose in the 6 months prior to the index date.

Criteria	Definition
	Cumulative dose will be calculated as the sum, across all fills, of [Strength x QD x Corticosteroid equivalent dose on each fill; only applied to oral glucocorticoids.
6. No more than one glucocorticoid injection/IV between index date +90 days and index date + end of follow up (180 days and 365 days after index date), inclusive.	Cannot receive glucocorticoid injections/ IV on more than one unique calendar day between the index date + 90 days and index date + end of follow up period (180 days and 365 days after the index date) inclusive
7. No use of pain medication class not observed during baseline period or at index.	Indicator for patients who initiated therapy during the 6 month and 12-month follow-up period with a new pain medication that they were not already taking during pre-index period or used as a concomitant medication with the index treatment. Pain medications initiated on or during the first 30 days after the index date will be considered to be used in concomitance with the index advanced treatment and will not be considered to be an addition of a new pain medication. Classes include opioids, NSAIDs, non-narcotic analgesics, anticonvulsants, antidepressants, and topical pain medications. Both medical and pharmacy claims will be assessed.
8. No use of spinal procedure for AS	Indicator for claims for spinal procedures at any time during the 6 month and 12 month follow-up periods. This will be assessed in medical claims only.

Criteria for bDMARD-naïve PsA Cohort:

Criteria	Definition
1. High adherence to index treatment	**Proportion of days covered (PDC)≥ 80%** PDC will be calculated as the ratio of the total number of days with drug at hand to the length of the time period under investigation (180 and 365 days). Total number of days with drug at hand was calculated as follows: 1) For outpatient Rx claims, the days' supply

Criteria	Definition
	values were summed across all claims for the index drug. 2) For medical claims, days' supply was equal to the labelled maintenance frequency (SC = subcutaneous, IV = intravenous): a. Adalimumab: 14 days (SC) b. Certolizumab: 28 days (SC) c. Etanercept: 7 days (SC) d. Golimumab: 56 days (IV), 28 days (SC) e. Infliximab: 56 days f. Ixekizumab: 28 days (SC) g. Secukinumab: 28 days (SC) h. Tofacitinib: 1 day (Tab) In both cases, overlapping days' supply across fills were subtracted from the total (with total Rx overlapping days across all fills being capped at 14 days; no cap for medical claims)
2. No switching/adding another non-index advanced PsA therapy	Patients who initiate other non-index advanced therapy medications during follow-up period (180 and 365 days). Advanced PsA therapy will include: tofacitinib, upadacitinib, adalimumab, golimumab, infliximab, etanercept, certolizumab, ixekizumab, secukinumab, ustekinumab, risankizumab or guselkumab, abatacept, apremilast, deucravacitinib, bimekizumab, brodalumab
3. **No dose escalation or increased frequency of the index advanced therapy**	Dose escalation will be assessed by comparing the first observed maintenance dose for the index advanced therapy after loading to all doses observed during the remainder of follow-up. If any dose is 20% higher than the maintenance index dose, the patient will be flagged as having escalated their dose. Only the index advanced therapy will be assessed. Dose was calculated as follows: 1. For outpatient Rx claims: Dose = (Strength x Quantity Dispensed (QD))/Days' supply 2. For medical claims: Dose = (Strength based on HCPCS code) x (Billed

Criteria	Definition
	units) (The total dosing amount will be used without considering the time window between two administrations.) For patients who only receive IV administrations, the number of claims will also be calculated . This frequency must be within 120% of the number expected during 1 year time period based on guidelines. For patients who only receive IV administrations, upon sufficient sample size, a sensitivity analysis, assessing dose escalation based on both the frequency of administration and dosage change may be considered for the subset of patients with available dosage information.
4. No addition of new csDMARD for PsA not already taken during baseline period or at index.	Between the index+30 days and end of the study period (at 6 months or 12 months after the index date), patient cannot initiate therapy with a new conventional DMARD (methotrexate, sulfasalazine, leflunomide or hydroxychloroquine) that they were not already taking during the 6 months prior to the index date or used as a concomitant medication with the index treatment. csDMARDs initiated on or during the first 30 days after the index date will be considered to be used in concomitance with the index advanced treatment and will not be considered to be an addition of a new csDMARD.
5. No increase in dose of oral glucocorticoid compared with baseline.	For patients who received no prescriptions for oral glucocorticoids during the 6 months prior to the index date, cannot have received more than 30 days of oral glucocorticoids between the index date + 90 days and the end of the study period (6 months or 12 months after the index date), inclusive. <u>Analysis at 6 months:</u> For patients who received prescriptions for oral glucocorticoids in the 6 months prior to the index

Criteria	Definition
	date, the cumulative glucocorticoid dose in the last 3 months prior to the end of the study period must be similar (that is, within 120%) to the cumulative dose in the last 3 months prior to the index date. <u>Analysis at 12 months:</u> For patients who received prescriptions for oral glucocorticoids in the 6 months prior to the index date, the cumulative glucocorticoid dose in the 6 months prior to the end of the study period must be similar (that is, within 120%) to the cumulative dose in the last 6 months prior to the index date. Cumulative dose was calculated as the sum, across all fills, of [Strength x QD x Corticosteroid equivalent dose on each fill; only applied to oral glucocorticoids.
6. No more than one glucocorticoid injection/IV between index date +90 days and index date + end of follow up (180 days and 365 days after index date), inclusive.	Cannot receive glucocorticoid injections/ IV on more than one unique calendar day between the index date + 90 days and index date + end of follow up period (180 days and 365 days after the index date) inclusive
7. No use of new topical treatment, actinotherapy or oral retinoid (class level) not observed during baseline period or at index	Indicator for patients who initiated therapy during the 6 month and 12-month follow-up period with a new topical treatment, actinotherapy, or oral retinoid that they were not already taking during pre-index period or used as a concomitant medication with the index treatment. New topical treatment, actinotherapy or oral retinoid medications initiated on or during the first 30 days after the index date will be considered to be used in concomitance with the index advanced treatment and will not be considered to be an addition of a new medication.
8. No use of pain medication class not observed during baseline period or at index.	Indicator for patients who initiated therapy during 6 month and 12-month follow-up period with a new pain medication that they were not already taking during pre-index period or used as a concomitant medication with the index treatment. Pain medications initiated on or during the first 30

Criteria	Definition
	days after the index date will be considered to be used in concomitance with the index advanced treatment and will not be considered to be an addition of a new pain medication. Classes include opioids, NSAIDs, non-narcotic analgesics, anticonvulsants, antidepressants, and topical pain medications. Both medical and pharmacy claims will be assessed.

Outcome variables that will be assessed

The number and proportion of patients that satisfy the effectiveness criteria.

Primary Outcome:

- Patients that satisfy all the 8 effectiveness criteria

Secondary Outcome:

- Patients that satisfy each of the effectiveness criterion – pending feasibility

Additional secondary outcomes of this study are persistence, HCRU, and costs. These will be assessed during the follow-up period:

Persistence definition

Persistence on index therapy within 12 months of treatment initiation will be assessed. Persistence, defined as "duration of time from initiation to discontinuation of the index therapy", will be estimated (in months). Patients will be considered to have discontinued their index therapy (non-persistent) if a gap of ≥ 60 days is observed between the end of a prescription (including days of supply) and the start of the next prescription for the index therapy.

For medical claims, days' supply will be imputed according to the labelled maintenance frequency (SC = subcutaneous, IV = intravenous):

a. Adalimumab: 14 days (SC)

b. Certolizumab: 28 days (SC)

c. Etanercept: 7 days (SC)

d. Golimumab: 56 days (IV), 28 days (SC)

e. Infliximab: 56 days

f. Ixekizumab: 28 days (SC)

g. Secukinumab: 28 days (SC)

h. Tofacitinib: 1 day (Tab)

HCRU and Costs

All cause and AxSpA-related HCRU and costs within 6 and 12 months of index treatment initiation will be assessed: (Unit: per patient per month; See Table 1 & Table 2 for the definition of each variable).

HCRU

- All-cause:
  - # of Emergency department (ED) visits
  - # of Hospitalizations (inpatient stays)
    - Length of stay (LOS)
  - # of Rheumatologist visits
  - # of Outpatient visit (excludes ED visit; may provide breakdown in categories like ambulatory surgical center, hospital outpatient department, office visits, etc. if data permit)
  - # of Prescription fills
- AxSpA-related: the below will be considered AxSpA-related if the record had a diagnosis of AxSpA
  - # of AxSpA-related emergency department (ED) visits
  - # of AxSpA-related hospitalizations (inpatient stays)
  - # of AxSpA-related rheumatologist visit
  - # of AxSpA-related outpatient visit (excludes ED visit cost; may provide breakdown in categories like ambulatory surgical center, hospital outpatient department, office visits, etc. if data perm)
- # of AxSpA-related prescription fill

Costs

- All-cause:
  - Emergency department (ED) visits cost
  - Hospitalizations (inpatient stays) cost
  - Rheumatologist visit cost
  - Outpatient cost (excludes ED visit cost; may provide breakdown in categories like ambulatory surgical center, hospital outpatient department, office visit costs, etc. if data permit)
  - Pharmacy cost
  - Total medical cost
  - Total cost
- AxSpA-related: the below were considered AxSpA-related if the record had a diagnosis of AxSpA
  - AxSpA-related emergency department (ED) visits cost
  - AxSpA-related hospitalizations (inpatient stays) cost
  - AxSpA-related rheumatologist visit cost
  - AxSpA-related outpatient cost (excludes ED visit cost; may provide breakdown in categories like ambulatory surgical center, hospital outpatient department, office visit costs, etc. if data perm)
- AxSpA-related treatment administration cost
- AxSpA-related pharmacy cost
- Total cost for AxSpA-related treatment administration and pharmacy cost
- AxSpA-related total medical cost
- AxSpA-related total cost
- All costs will be adjusted to 2023 US dollars using the annual medical care component and drug cost component of the Consumer Price Index.

9.4. Data Sources

Komodo's Healthcare Map database is a large US administrative claims database which includes longitudinal information on patients' demographics, medical history, medication use, and healthcare utilization and costs. The claims data is mainly sourced from commercial, Medicaid and Medicare Advantage health plans covering more than 330 million lives over time across the United States. In the Komodo's Healthcare Map database, diagnoses, procedures, and prescription drugs are coded using the International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9/10-CM), the Current Procedural Terminology, Fourth Edition (CPT-4), Healthcare Common Procedure Coding System (HCPCS) codes and National Drug Code (NDC).

9.5. Study Size

9.5.1. PsA bDMARD Naive Cohort:

Preliminary feasibility analysis indicates a sample size range of approximately 600 patients on tofacitinib who are bDMARD naive, approximately 30,000 patients on TNFi and approximately 10,000 patients on Il-17i with continuous health care plan enrollment at least 365 days after index date.

9.5.2. AxSpA Cohort:

Preliminary feasibility analysis indicates a sample size range of approximately 600 patients on tofacitinib, approximately 8,000 patients on TNFi and approximately 2,000 patients on Il-17i with continuous health care plan enrollment at least 180 days after index date.

9.6. Data Management

This study will use retrospective data from the Komodo's Healthcare database - all study data exists in the structured form by the time of the study. Data will be accessed via the Komodo Sentinel Platform, which is a virtual Windows desktop, that is maintained and securely managed by Komodo – access is only provided by Komodo to authorized users. Analyses will be conducted using statistical software such as SAS, R, SQL and/or Python. Versions of packages will be documented to assure reproducibility. An analytical dataset comprising all records required for planned analyses will be created from the information contained exclusively within the Komodo's Healthcare database. The analytic file will include de-identified person-level data, and will include information on baseline and patients' characteristics, study outcomes and health plan enrolment dates. Analyses for this study will be conducted Redacted

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major

modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

All analyses will be done separately by indication.

Propensity-score (PS) methods will be employed. PS will be estimated for index medication class (ie, tofacitinib, TNFi, IL-17i) for each patient's exposure -allowing for multiple exposures (multiple index dates/medications) per patient over the study period for the AxSpA sample. Only patients in the AxSpA sample will be allowed to have multiple index dates/medications as the analyses for PsA will be limited to the subset of b/tsDMARD-naïve patients. Variables assessed for inclusion in the PS estimation model will follow those listed in Table 1, Table 2 and Table 3 (depending upon indication), especially those noted as "Baseline characteristics and potential confounder". Other independent variables may also be assessed. For patients in the AxSpA sample, baseline characteristics will be assessed at the time of each treatment initiation (each index date).

Weighted (ie, inverse probability of treatment weighting, IPTW) time-to-event analyses (eg, Cox proportional hazards) will compare failure of the effectiveness criteria, for the index medication classes (TNFi or IL-17i) versus tofacitinib. Estimates (eg, hazard ratios) with 95% CIs will be provided.

Weighted (IPTW) generalized linear models (GLM) (or two-part model) with for instance Generalized Estimating Equations (GEE) for correlated data (for the AxSpA sample) will be applied for continuous measures (eg, Poisson distribution for count measures and gamma distribution for costs).

In addition, the following sensitivity analyses, using a modified claims-based algorithm will be performed:

a. Excluding criterion 1 (high adherence) to avoid bias estimating adherence of drugs with different administration routes using health claims.

b. Second, exclude criterion 3 (no increase in dose or frequency of index drug), because patients starting therapy with tofacitinib, and some biologics usually do not change the initial dose and/or the frequency.

c. Criteria 5 will be updated to use a cutoff of 50% (instead of 20%) to identify increase in dose of oral glucocorticoid

d. Exclude criterion 5 due to shorter time for outcome measure for the analyses at 6 months

e. Criteria 3: For patients who only receive IV administrations, upon sufficient sample size, a sensitivity analysis, assessing dose escalation based on both the frequency of administration and dosage change may be considered for the subset of patients with available dosage information.

Depending on the extent of missing data, multiple imputation methods may be undertaken. Missing data methods are fully described in the SAP.

Secondary outcomes of drug persistence, HCRU and cost will be further defined and elaborated from an analysis perspective within the SAP.

9.8. Quality Control

Data in Komodo Healthcare Map database is collected in an electronic format. Komodo performs combinations of automated and manual data quality testing throughout the ingestion, transformation, data product development and maintenance life cycle. Analyses will be programmed according to the specifications in the protocol and documented in a statistical analysis plan/programming plan. All cohorts developed, statistical analyses implemented, and tables completed will undergo quality control review by at least one additional analyst or scientist under the supervision of the Study Lead. The Study Lead will review all results tables and other final deliverables to confirm accuracy, logical flow, and appropriate format.

9.9. Strengths and Limitations of the Research Methods

Komodo is a large dataset with a fair geographic coverage, however, administrative claims databases are not primarily designed for research purposes; therefore, some relevant patient and disease characteristics may be unknown/missing, misclassified, or underestimated. Treatment or disease management data may be missing due to patients paying out-of-pocket. Some relevant concomitant medications may be accessed over the counter (OTC), such as pain medications, and may not be captured in the claims data. While claims data denote the date of fills and days' supply, information on the actual adherence to prescribed medications is not available.

The study includes only those patients who have at least 6 or 12 months of continuous enrollment after index date to ensure there is sufficient time to assess the study outcomes in the AS and PsA groups, respectively. This criterion may introduce bias by including patients with less severe disease as those who did not meet the enrollment criteria, for reasons such as death or loss of health care coverage will not be included.

AxSpA or PsA disease severity may not be accurately assessed using claims database due to lack of information on such as laboratory data and clinical notes. Surrogate measures (based on demographics, healthcare utilization, comorbidities, and medication history) will be used as proxies for severity in this study.

The specific reasons for initiating treatment and reasons for changes in treatment (discontinuation/switching) are not available in a claims database. It is possible that some of the study treatments analyzed were prescribed for other conditions. In addition, it is possible that patients who discontinued their medication due to remission and switched medications due to unavailability of prior medications could be misclassified as treatment ineffective.

Other limitations that are general to all claims database analyses as well as those specific to this study should be noted. Diagnosis of AxSpA and PsA will be identified using ICD diagnosis codes, which are subject to potential miscoding, though presumably without respect to the treatment or outcomes.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

This study is a retrospective, non-interventional study that will use secondary anonymized data provided by Komodo. Komodo data are de-identified and provisions are in place to prevent re-identification in order to protect patients' confidentiality. This study was submitted to an IRB and an exception letter was received.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) and Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

One or more abstracts may be developed and submitted to relevant scientific conference(s) and one or more manuscripts may be developed and submitted to relevant peer-reviewed medical journals. Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential conflicts of interest will be disclosed.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from participants is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

1. Sieper J, Braun J, Dougados M et al (2015) Axial spondylarthritis. Nat Rev Dis Primers 1:15013.

2. Gossec L, Smolen JS, Ramiro S et al (2016) European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 75:499–510.

3. Ogdie A, Weiss P (2015) The epidemiology of psoriatic arthritis. Rheum Dis Clin North Am 41:545–568.

4. Gelfand JM, Gladman DD, Mease PJ et al (2005) Epidemiology of psoriatic arthritis in the population of the United States. J Am Acad Dermatol 53:573.

5. Asgari MM, Wu JJ, Gelfand JM et al (2013) Validity of diagnostic codes and prevalence of psoriasis and psoriatic arthritis in a managed care population, 1996–2009 Pharmacoepidemiol Drug Saf 22:842–849.

6. Datta D, Podder I, De A et al (2022) Psoriatic Arthritis: A Comprehensive Update for Dermatologists with Review of Literature. Indian J Dermatol. 2022;67(4):381-386.

7. Haroon M, Gallagher P, FitzGerald O (2015). Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis, 74(6):1045-1050.

8. Singh JA, Guyatt G, Ogdie A et al (2019) Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis Rheumatol 71:5–32.

9. Ward MM, Deodhar A, Gensler LS et al (2019) 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol, 71:1599–1613.

10. Ward MM, Deodhar A, Akl EA et al (2016) American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Care Res 68:151–166.

11. Lee MP, Lii J, Jin Y et al (2018) Patterns of systemic treatment for psoriatic arthritis in the US: 2004–2015. Arthritis Care Res 70:791–796.

12. Coates LC, Kavanaugh A, Mease PJ et al (2016) Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheumatol 68:1060–1071.

13. Zhu B, Edson-Heredia E, Gatz JL et al (2013) Treatment patterns and health care costs for patients with psoriatic arthritis on biologic therapy: a retrospective cohort study. Clin Ther 35:1376–1385.

14. Davis JC Jr, Van Der Heijde D, Braun J et al (2003) Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum 48:3230–3236.

15. Xeljanz®, Labeling-Package Insert Label, FDA website https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/203214s034,208246s021,213082s006lbl.pdf, *accessed on June, 28, 2024.*

16. Xeljanz®, Efficacy-New Indication Letter, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/203214Orig1s017,208246ORig1s003ltr.pdf, *accessed on June, 28, 2024.*

17. Xeljanz®, Efficacy-New Indication Letter, Website https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/203214Orig1s028;208246Orig1s013;213082Orig1s003ltr.pdf, *accessed on June, 28, 2024.*

18. Mease P, Hall S, Fitzgerald O et al (2017). Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med, 377:1537–1550.

19. McInnes IB, Nash P, Ritchlin C, et al. Secukinumab for psoriatic arthritis: comparative effectiveness versus licensed biologics/apremilast: a network meta-analysis. J Comp Eff Res 2018;7:1107–23.

20. Kawalec P, Holko P, Moćko P, et al. Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis. Rheumatol Int 2018;38:189–201.

21. Zhang H, Wen J, Alexander GC, et al. Comparative effectiveness of biologics and targeted therapies for psoriatic arthritis. RMD Open 2021;7:e001399. doi:10.1136/rmdopen-2020-001399.

22. Curtis JR, Baddley JW, Yang S, et al. Derivation and preliminary validation of an administrative claims-based algorithm for the effectiveness of medications for rheumatoid arthritis. Arthritis Res Ther 2011;13:R155.

23. Hunter T, Grabner M, Birt J, et al. Identifying inadequate response among patients with ankylosing spondylitis and psoriatic arthritis prescribed advanced therapy in a real-world, commercially insured adult population in the USA. Clin Rheumatol. 2022 Sep;41(9):2863-2874.

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FRO STUDY PROTOCOL

Not required

ANNEX 3. ADDITIONAL INFORMATION

Table 1 – ICD-10 Codes to Identify AxSpA

ICD-10 codes	Code description
M45	**Ankylosing spondylitis of multiple sites in spine**
M45.0	Ankylosing spondylitis of occipito-atlanto-axial region
M45.1	Ankylosing spondylitis of cervical region
M45.2	Ankylosing spondylitis of cervicothoracic region
M45.3	Ankylosing spondylitis of thoracic region
M45.4	Ankylosing spondylitis of thoracolumbar region
M45.5	Ankylosing spondylitis lumbar region
M45.6	Ankylosing spondylitis of lumbosacral region
M45.7	Ankylosing spondylitis sacral and sacrococcygeal region
M45.8	Ankylosing spondylitis of unspecified sites in spine
M45.9	Ankylosing spondylitis of multiple sites in spine
M45.A	**M45.A Non-radiographic axial spondyloarthritis [Non-Specific Code]**
M45.A0	Non-radiographic axial spondyloarthritis of unspecified sites in spine
M45.A1	Non-radiographic axial spondyloarthritis of occipito-atlanto-axial region
M45.A2	Non-radiographic axial spondyloarthritis of cervical region
M45.A3	Non-radiographic axial spondyloarthritis of cervicothoracic region
M45.A4	Non-radiographic axial spondyloarthritis of thoracic region
M45.A5	Non-radiographic axial spondyloarthritis of thoracolumbar region
M45.A6	Non-radiographic axial spondyloarthritis of lumbar region
M45.A7	Non-radiographic axial spondyloarthritis of lumbosacral region
M45.A8	Non-radiographic axial spondyloarthritis of sacral and sacrococcygeal region
M45.AB	Non-radiographic axial spondyloarthritis of multiple sites in spine
M46.0	**Spinal enthesopathy**
M46.00	Spinal enthesopathy, site unspecified
M46.01	Spinal enthesopathy, occipito-atlanto-axial region
M46.02	Spinal enthesopathy, cervical region
M46.03	Spinal enthesopathy, cervicothoracic region
M46.04	Spinal enthesopathy, thoracic region
M46.05	Spinal enthesopathy, thoracolumbar region
M46.06	Spinal enthesopathy, lumbar region
M46.07	Spinal enthesopathy, lumbosacral region
M46.08	Spinal enthesopathy, sacral and sacrococcygeal region
M46.09	Spinal enthesopathy, multiple sites in spine
M46.1	**Sacroiliitis, not elsewhere classified**
M46.8	**Other specified inflammatories spondylopathies**
M46.80	Other specified inflammatories spondylopathies - site unspecified
M46.81	Other specified inflammatories spondylopathies - occipito-atlanto-axial region

ICD-10 codes	Code description
M46.82	Other specified inflammatories spondylopathies, cervical region
M46.83	Other specified inflammatories spondylopathies, cervicothoracic region
M46.84	Other specified inflammatories spondylopathies, thoracic region
M46.85	Other specified inflammatories spondylopathies, thoracolumbar region
M46.86	Other specified inflammatories spondylopathies, lumbar region
M46.87	Other specified inflammatories spondylopathies, lumbosacral region
M46.88	Other specified inflammatories spondylopathies, sacral and sacrococcygeal region
M46.89	Other specified inflammatories spondylopathies, multiple sites in spine
M46.9	**Unspecified inflammatory spondylopathy**
M46.90	Unspecified inflammatory spondylopathy, site unspecified
M46.91	Unspecified inflammatory spondylopathy, occipito-atlanto-axial region
M46.92	Unspecified inflammatory spondylopathy, cervical region
M46.93	Unspecified inflammatory spondylopathy, cervicothoracic region
M46.94	Unspecified inflammatory spondylopathy, thoracic region
M46.95	Unspecified inflammatory spondylopathy, thoracolumbar region
M46.96	Unspecified inflammatory spondylopathy, lumbar region
M46.97	Unspecified inflammatory spondylopathy, lumbosacral region
M46.98	Unspecified inflammatory spondylopathy, sacral and sacrococcygeal region
M46.99	Unspecified inflammatory spondylopathy, multiple sites in spine

Table 2 – ICD-10 codes to identify PsA

ICD-10 codes	Code description
L40.5	**Arthropathic psoriasis [Non-Specific Code]**
L40.50	Arthropathic psoriasis, unspecified
L40.51	Distal interphalangeal psoriatic arthropathy
L40.52	Psoriatic arthritis mutilans
L40.53	Psoriatic spondylitis
L40.54	Psoriatic juvenile arthropathy
L40.59	Other psoriatic arthropathy

Document Approval Record

Document Name:	A3921446_Protocol_V1 FINAL_23AUG2024
Document Title:	A3921446_Protocol_V1 FINAL_23AUG2024

Redacted	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]