NON-INTERVENTIONAL (NI)/LOW-INTERVENTIONAL STUDY TYPE 1 (LIS1) STUDY REPORT

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	[redacted]
Version identifier of the study report	Version 1.0
Date	04 June 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000226
Active substance	[redacted] – tofacitinib citrate
Medicinal product	[redacted]® (Tofacitinib)
Research question and objectives	Research questions: How does real-world treatment effectiveness compare among axial spondylarthritis (AxSpA) and biologic or targeted synthetic disease-modifying anti-rheumatic drug (b/tsDMARD)-naïve psoriatic arthritis (PsA) patients treated with tofacitinib, tumour necrosis factor inhibitor (TNFi), and interleukin 17 inhibitor (IL-17i)? How do the rates of drug persistence for AxSpA and b/tsDMARD-naïve 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-naïve 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 population 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 population 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 population 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-naïve PsA patients within 12 months of treatment with tofacitinib vs. TNFi vs. IL-17i – among the population 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 population of patients with at least 6 months or 12 months of continuous enrollment after index date, respectively.
Country of study	United States
Author	[redacted]

[redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

Tables

Figures

Annex 1. List of stand-alone documents

Appendix 1. SIGNATURES
[redacted]SIGNATURES_10MAR2026

Appendix 2. Protocol

[redacted]NON-INTERVENTIONAL STUDY PROTOCOL_V3.0_10JUL2025

Appendix 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)
Not applicable.

Appendix 3.1. List of Investigators by Country
Not applicable.

Appendix 3.2. List of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and Corresponding Protocol Approval Dates
Not applicable.

Appendix 4. STATISTICAL ANALYSIS PLAN
[redacted]Statistical Analysis Plan (SAP)_Version 2.3_12MAY2025

Appendix 5. SAMPLE CASE REPORT FORM (CRF)/DATA COLLECTION TOOL (DCT)
Not applicable.

Appendix 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)
Not applicable.

Appendix 7. LIST OF SUBJECT DATA LISTINGS

[redacted]Study Results Workbook

Appendix 7.1 Withdrawn Subjects
Not applicable.

Appendix 7.2 Protocol Deviations
Not applicable.

Appendix 7.3 Subjects Excluded from the Analysis
Information regarding subjects excluded from the analysis may be seen in Table 1a & 1b in the Excel Study Results Workbook:

[redacted]Study Results Workbook

Appendix 7.4 Demographic Data
Information regarding demographic data may be seen in Table 2a & 2b (for the AxSpA sample), and Table 2c & 2d (for the PsA sample), in the Excel Study Results Workbook:

[redacted]Study Results Workbook

Appendix 7.5 Medication/Treatment Data

Information regarding medication/treatment data may be seen in Table 3a & 3b (for the AxSpA sample), and Table 3c & 3d (for the PsA sample), in the Excel Study Results Workbook:

[redacted]Study Results Workbook

Appendix 7.6 Endpoint Data

Information regarding endpoint data may be seen in Table 4a & 5a, Table 4b & 5b, Table 6b & Figure 1b, Table 7a & 7b (for the AxSpA sample), and Table 4c & 5c, Table 4d & 5d, Table 6d & Figure 1d (for the PsA sample), in the Excel Study Results Workbook:

[redacted]Study Results Workbook

Appendix 7.7 Adverse Events

Not applicable.

Appendix 7.8 Laboratory listings

Not applicable.

Appendix 8. ADDITIONAL DOCUMENTS

Not applicable.

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
aHR	Adjusted Hazard Ratio
AS	Ankylosing Spondylitis
AxSpA	Axial Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
b/tsDMARD	Biologic Or Targeted Synthetic Disease-Modifying Anti-Rheumatic Drug
CI	Confidence Interval
CPT	Current Procedure Terminology
csDMARD	Conventional Synthetic Disease-Modifying Antirheumatic Drug
DAS	Disease Activity Score
ED	Emergency Department
FDA	Food And Drug Administration
GC	Glucocorticoid
HCPCS	Healthcare Common Procedure Coding System
HCRU	Healthcare Resource Utilization
HMA-EMA	Heads Of Medicines Agencies (HMA) And The European Medicines Agency (EMA)
HR	Hazard Ratio
ICD-10	International Classification of Diseases – Tenth Revision
IEC	Independent Ethics Committee
IL-17i	Interleukin-17 Inhibitor
IQR	Interquartile Range
IRB	Institutional Review Board
IV	Intravenous
JAKi	Janus Kinase Inhibitors
LDA	Low Disease Activity
NDC	National Drug Center
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over-The Counter
PASS	Post Authorization Safety Study
PDC	Proportion Of Days Covered
PPPM	Per Patient Per Month
PPPY	Per Patient Per Year
PS	Propensity Score
PsA	Psoriatic Arthritis
QC	Quality Control
RA	Rheumatoid Arthritis
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SMD	Standardized Mean Difference
TNFi	Tumour Necrosis Factor Inhibitor
US	United States

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	31 January 2025	18 February 2025	Minor delay due to finalization of study protocol and SAP
End of data collection	15 June 2025	07 August 2025	Minor delay due to programming and iterations reviewing preliminary results.
Registration in the HMA-EMA Catalogues of RWD Studies	28 October 2024	15 November 2024	Slight delay due to internal processes taking longer than expected.
Final report of study results	15 May 2026	30 June 2026	Slight delay due to previous delays in end of data collection and programming

6. RATIONALE AND BACKGROUND

Ankylosing spondylitis (AS), also referred to as radiographic axial spondyloarthritis (AxSpA), and psoriatic arthritis (PsA) are immune-mediated diseases characterized by chronic inflammation within the musculoskeletal system. AxSpA affects 0.20%-1.00% of the United States (US) population and leads to spinal stiffness and reduced mobility.[1-3] PsA, a seronegative spondylarthritis, affects 0.05%-0.25% of the US population and affects joints and skin, occurring in up to 30% of psoriasis patients.[1,2,4,5] Axial involvement may occur in up to 50% of patients with PsA.[6]

Management of AxSpA and PsA focuses on alleviating symptoms, slowing disease progression, and enhancing patient health-related quality of life.[7] Historically, first-line therapies included non-steroidal anti-inflammatory drugs (NSAIDs) for AxSpA and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) for PsA.[8,9] For patients with inadequate response to conventional therapies, advanced treatments are available, including phosphodiesterase 4 inhibitors, tumor necrosis factor inhibitors (TNFi), interleukin-17 and interleukin-23 inhibitors (IL-17i, IL-23i), and Janus Kinase inhibitors (JAKi).[10-14]

JAKi are oral small molecule drugs with rapid onset of action, a short half-life, and lack of immunogenicity when compared to biologic therapies. Tofacitinib is a JAKi approved in the US for several inflammatory conditions, including AS (radiographic AxSpA) and PsA.[15] Tofacitinib received approval by the US Food and Drug Administration (FDA) for PsA on 14 December 2017 and for AS on 14 December 2021.[16,17]

The therapeutic landscape for AxSpA and PsA has continued to expand. However, direct comparative clinical data between advanced therapies remain limited, as head-to-head randomized clinical trials are rare and many existing studies are not powered for formal direct comparisons.[18] While randomized controlled trials and systematic reviews offer important efficacy and safety information, assessment of treatment effectiveness in everyday clinical practice through real-world studies is essential.[19,20]

A recent study by Zhang, et al. assessed the comparative effectiveness of various advanced therapies using a claims-based algorithm in an administrative database.[21] However, comparative studies specifically including tofacitinib for AxSpA and PsA using this algorithm, that originally characterized effectiveness of treatments for rheumatoid arthritis (RA) (which may also be used for AxSpA), are lacking.[22,23]

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Research Questions

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

1. How does real-world treatment effectiveness compare among AxSpA and biologic or targeted synthetic disease-modifying anti-rheumatic drug (b/tsDMARD)-naïve PsA patients treated with tofacitinib, TNFi, and IL-17i?

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

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

7.2. Primary Objectives

The primary objectives for this study were:

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-naïve 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.

7.3. Secondary Objectives

The secondary objectives for this study were:

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 cohort 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 cohort 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 cohort 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-naïve PsA patients within 12 months of treatment with tofacitinib vs. TNFi vs. IL-17i – among the cohort 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 cohort of patients with at least 6 months or 12 months of continuous enrollment after index date, respectively.

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
Version 1.0	23 August 2024	Substantial	Section 4 Section 9.2.2	Update of exclusion criteria for b/tsDMARD-naïve PsA cohort to also include: baricitinib as part of the JAK class and tildrakizumab as part of the IL-23i class	Additional drugs had to be added for completeness of the drug list
Version 1.0	23 August 2024	Substantial	Section 9.3.1	Removed “Other route of administration, N (%)” for steroid	Other route of administration was not meaningful for the studied diseases
Version 1.0	23 August 2024	Substantial	Section 9.3.1 Section 9.3.2	Removed chloroquine and hydroxychloroquine from the list of csDMARDs	Chloroquine and hydroxychloroquine were removed as not meaningful for the studied diseases
Version 1.0	23 August 2024	Substantial	Section 9.3.1 Section 9.3.2	Updated list of prior and post-index advanced medication to include baricitinib and tildrakizumab	Additional drugs had to be added for completeness of the drug list
Version 1.0	23 August 2024	Substantial	Section 4 Section 9.7	Added the following clarifying statement. If the Cox model is not feasible (e.g., the algorithm fails to converge), an acceptable alternative model is logistic regression	Clarification
Version 1.0	23 August 2024	Substantial	Section 9.1	Added the following clarifying statement before presenting Figure 1 and 2. *For illustration purposes, the calendar axis may not be proportional. The end of the follow up may be expanded if more recent data are available at the time of study start.	Clarification
Version 1.0	23 August 2024	Administrative	Section 4 Section 6	Planned dates were updated	Planned dates were updated to reflect the new data collection start date
Version 1.0	23 August 2024	Administrative	Section 14	The list of tables was included	The list of tables was added following comments from QC
Version 1.0	23 August 2024	Administrative	Section 15	The title for Table 2b was updated to match with the title used in Section 9	Correction. The title for Table 2b was updated to match with the title used in Section 9
Version 1.0	23 August 2024	Administrative	Table 2	Reference table number was added	Correction. Table number was missing from the text.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
Version 2.0	03 January 2025	Substantial	Abstract and Section 6. Milestones	End of data collection extended to 31-August 2025	Planned end date was updated to reflect the planned date of the end of the analyses.

9. RESEARCH METHODS

The research methods are described in the text which follows. The final protocol and Statistical Analysis Plan (SAP) can be found in Appendix 2 and Appendix 4, respectively.

9.1. Study Design

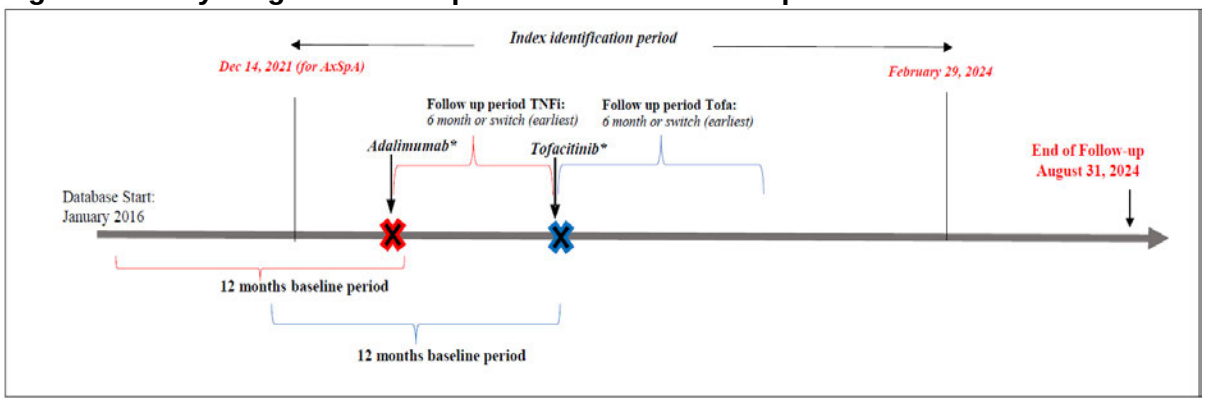
This non-interventional population-based retrospective cohort study analyzed a cohort of adults (aged ≥18 years) with AxSpA or PsA identified through a large US administrative claims database. The analyses were conducted separately for the AxSpA and PsA samples.

After identifying patients with indications of interest, all patients who met the inclusion and exclusion criteria listed under Section 8.3.1 and Section 8.3.2 were 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 were 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).

The baseline period was defined as 12 months prior to the index date. Patients' demographic and clinical characteristics were characterized at index date, baseline period, pre-index history, concomitant use (index date to index date + 30 days, inclusive), or recent use, depending on the study variable. Patients were 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.
Treatment effectiveness was assessed up to 6 and 12 months following the index date. HCRU and costs were assessed up to 6 and 12 months following the index date in the AxSpA sample. Persistence on the index treatment was assessed over the 12 months following the index date.

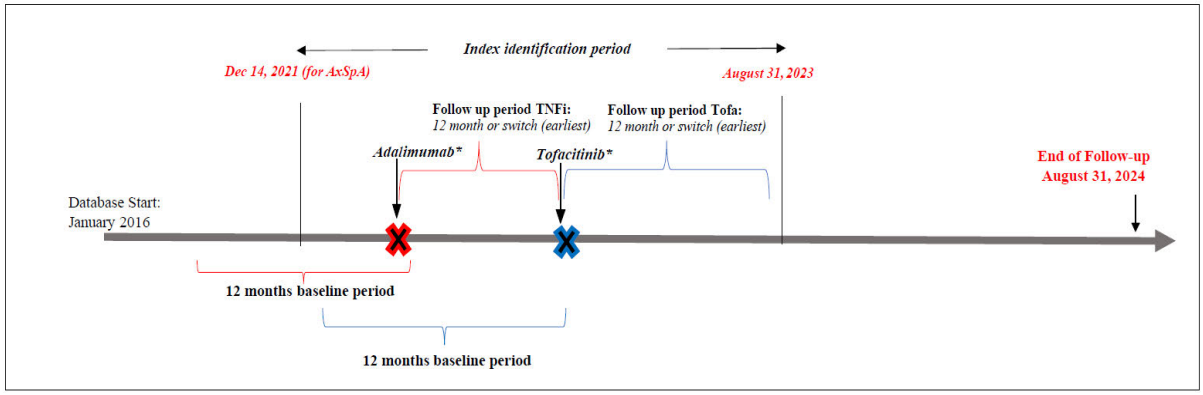
Figures 1-4 (below) show the study design schema.

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



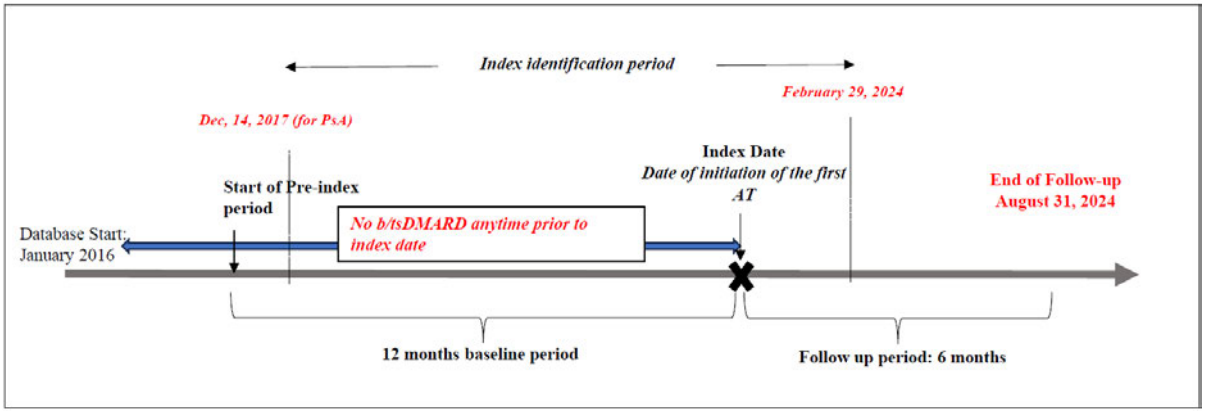
Note. **Only initiation of new advanced treatment (first time use) was considered to be a potential index date. First time use was defined as a prescription fill/administration for a drug for which we did not observe any prescription fill/administration at any time prior to the index date, using all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

Figure 2. Study Diagram for AxSpA – 12 Months Follow-up Period



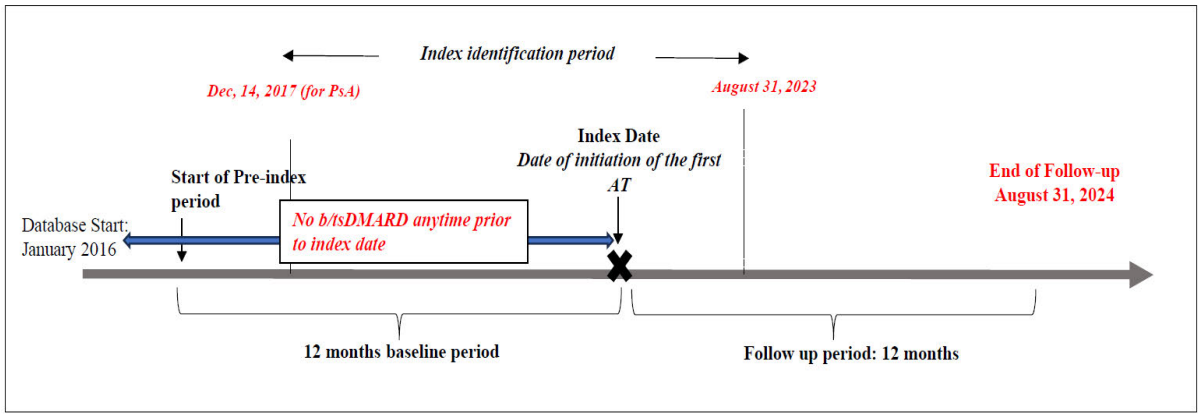
Note. **Only initiation of new advanced treatment (first time use) was considered to be a potential index date. First time use was defined as a prescription fill/administration for a drug for which we did not observe any prescription fill/administration at any time prior to the index date, using all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

Figure 3. Study Diagram for PsA b/tsDMARD-naïve – 6 Months Follow-up Period



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

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



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

9.2. Setting

De-identified individual patients who initiated one of the study advanced treatments were selected from the Komodo Healthcare database between 14 December 2021 and 29 February 2024 for the AxSpA 6-month population, 14 December 2017 and 29 February 2024 for the PsA 6-month population, 14 December 2021 and 31 August 2023 for the AxSpA 12-month population, and 14 December 2017 and 31 August 2023 for the PsA 12-month population.

The index date was defined as the date of initiation (first time use) for one of the selected advanced treatments (i.e., tofacitinib, TNFi, or IL-17i) within the specified identification period for each cohort. First time use was defined as a prescription fill/administration for a drug for which we did not observe any prescription fill/administration at any time prior to the index date, using all available data. For the AxSpA sample, patients may have had multiple index dates and contribute data to the study multiple times if they switched to another selected advanced treatment during the index identification period.

Patients' demographic and clinical characteristics were characterized at index date, baseline period, pre-index history, concomitant use (index date to index date + 30 days, inclusive), or recent use, depending on the study variable. History of comorbid conditions was assessed during the 12 months baseline period as well as using all historical data available for the patient. For patients with multiple index dates, there were multiple baseline periods - the patient's baseline status was reevaluated for each new index.

Patients were 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 was replicated for a subset of patients with at least 12 months of continuous enrollment after the index date.

Komodo Healthcare Map database (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 (i.e., estimated allowed amount). The claims data are mainly from commercial, Medicaid, and Medicare Advantage health plans covering more than 300 million lives over time across the US. Identification of disease populations, outcomes of interest, and drugs prescribed was implemented using International

Classification of Diseases – Tenth Revision (ICD-10) codes, current procedure terminology (CPT) procedure codes, Healthcare Common Procedure Coding System (HCPCS), and prescribing data (e.g., National Drug Center (NDC) codes) in the patients' records.

Exposure to therapies was defined using the NDC for dispensed medications and, where relevant, procedure codes (CPT/HCPCS) for injection or infusion. For both AxSpA and PsA samples, the initiation of a new treatment (first time use) was defined as a prescription fill/administration for a drug for which we did not observe any prescription fill/administration at any time prior to the index date, using all available data.

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

9.3. Subjects

The populations under study were adult patients who initiated one of the study advanced treatments between 14 December 2021 and 29 February 2024 for the AxSpA 6-month population, 14 December 2017 and 29 February 2024 for the PsA 6-month population, 14 December 2021 and 31 August 2023 for the AxSpA 12-month population, and 14 December 2017 and 31 August 2023 for the PsA 12-month population.

9.3.1. Inclusion Criteria

Patients had to 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 1 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.
3. Evidence of initiation (first time use) for at least 1 approved advanced treatment (see Table 1 of the SAP for a complete list of advanced treatments) during the identification period.
    a. The index date was defined as the date of initiation of a new advanced treatment (first time use) – index date identified over the index identification period.
        i. The initiation of a new treatment (first time use) was defined as a prescription fill/administration for a drug for which we did not observe any prescription fill/administration at any time prior to the index date, using all available data.
    b. For the AxSpA sample, patients may have contributed to multiple time segments of the study if they switched to another advanced medication (first time use) over the index identification period (i.e., 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 was replicated for the subset of patients with at least 12 months of continuous enrollment after index date (including index date).

9.3.2. Exclusion Criteria

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

1. Combination therapy, with more than 1 advanced therapy prescribed simultaneously on index date (i.e., 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-Naïve PsA sample:

1. Patients with ≥1 claim for any of the treatments below any time prior to the index date:
    a. Includes JAKi (tofacitinib, upadacitinib, baricitinib), PDE4 inhibitor (apremilast), IL-12/-23i (ustekinumab), TNFi (adalimumab, golimumab, infliximab, etanercept, certolizumab), IL-17i (ixekizumab, secukinumab, brodalumab, bimekizumab), IL-23i (risankizumab or guselkumab, tildrakizumab), CTLA-4i (abatacept), TYK2 (deucravacitinib).

9.4. Variables

Variables for exposure, outcomes, demographics, and clinical characteristics of interest are included below. Detailed operational definitions, including code lists and time periods of interest where applicable, as well as a full list of baseline characteristics and covariates, are provided in the SAP.

Table 2. List of Exposure Variables and Baseline Characteristics for Both Cohorts

Variable	Role	Operational definition
Tofacitinib	Exposure (treatment variable)	Use of tofacitinib on index date
TNFi	Exposure (treatment variable)	Use of TNFi (adalimumab, golimumab, infliximab, etanercept, or certolizumab) on index date
IL-17i	Exposure (treatment variable)	Use of IL-17i (ixekizumab or secukinumab) on index date
Time since prior advanced treatment – only applicable for the AxSpA sample	Baseline characteristic and potential confounder	Among those who used at least one advanced medication prior to index, time between last days of supply/administration for the last prescription for a b/tsDMARD before index date and index date.

Variable	Role	Operational definition
Duration of continuous enrollment before index date	Baseline characteristic	Time between start of continuous enrollment and index date, in days
Age at index	Baseline characteristics and potential confounder	Age was 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	Sex was defined as either male or female as of the index date
Year of index date	Baseline characteristics and potential confounder	Year of index date
Insurance type	Baseline characteristics and potential confounder	Patient's insurance type as of the index date e.g., Commercial, Medicare and Other
US geographic region	Baseline characteristics and potential confounder	The US was divided into five regions: Northeast, South, Midwest, West and unknown.

Table 3. List of Baseline Variables specific to the AxSpA cohort

Variable	Role	Operational definition
Prior use of advanced medications	Baseline characteristics and potential confounder	Advanced medications included: tofacitinib, upadacitinib, baricitinib, apremilast, adalimumab, golimumab, infliximab, etanercept, certolizumab, ixekizumab, secukinumab, deucravacitinib, bimekizumab, brodalumab, tildrakizumab Use of advanced treatments any time prior to index date; binary (yes/no).
Healthcare resource utilization – specialty visits	Baseline characteristics	Specialty visits during the 365 days baseline period were assessed including: • 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 were defined as visits associated with a diagnosis code for AxSpA.
Healthcare resource utilization– all cause and AxSpA-related	Baseline characteristics	Healthcare resource utilization during the 365 days baseline period was assessed. AxSpA related visits were defined as visits associated with a diagnosis code for AxSpA. These included the following: • All-cause inpatient admissions ○ Patients with any inpatient admissions, N (%) ○ Number of all-cause inpatient admissions among all patients ○ Length of all-cause inpatient admissions in days • AxSpA-related inpatient admissions ○ Patients with any AxSpA-related inpatient admissions, N (%) ○ Number of AxSpA-related inpatient admissions among all patients ○ Length of AxSpA-related inpatient admissions in days • Number of emergency department (ED) visits ○ All-cause ED visits ▪ Patients with any ED visits, N (%) ▪ Number of all-cause ED visits among all patients ○ AxSpA-related ED visits ▪ Patients with AxSpA-related ED visits, N (%) ▪ Number of AxSpA-related ED visits among all patients • Number of outpatient visits (e.g., includes physician office visits, walk-in retail health clinic visits, and urgent care facility visits) ○ All-cause outpatient visits (excludes ED visit) ▪ Patients with all-cause outpatient visits, N (%) ▪ Number of all-cause outpatient visits among all patients ○ 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)

		○ All-cause prescription ▪ Patients with all-cause prescription, N (%) ▪ Number of all-cause prescriptions among all patients ○ AxSpA-related prescription ▪ Patients with AxSpA-related prescription, N (%) ▪ Number of AxSpA-related prescription (csDMARDs, advanced treatment (i.e., b/tsDMARDs), NSAIDs, steroid, opioids) among all patients
Costs – all cause and AxSpA-related	Baseline characteristics	Cost of healthcare resource utilization during the 365 days baseline period was assessed based on allowed amounts. AxSpA related costs were defined as costs associated with a diagnosis code for AxSpA in any position. These included the following: • All-cause inpatient costs ○ Costs of all-cause inpatient visits among all patients • All-cause rheumatology visit costs ○ Costs of all-cause rheumatology visits among all patients • All-cause ED costs ○ Costs of all-cause ED visits among all patients • All-cause outpatient costs (excludes ED costs) ○ Costs of all-cause outpatient visits among all patients • All-cause pharmacy costs ○ Costs of all-cause outpatient prescription of medicine among all patients • All-cause total medical costs ○ Costs of all-cause HCRU among all patients. (sum of inpatient, ED, and outpatient costs) • All-cause total costs Costs of all-cause HCRU among all patients. (sum of inpatient, ED, outpatient, and pharmacy costs) • AxSpA-related inpatient costs ○ Costs of AxSpA-related inpatient visits among all patients • AxSpA-related ED costs ○ Costs of AxSpA-related ED visits among all patients • AxSpA-related outpatient costs

		○ Costs of AxSpA-related outpatient visits among all patients • AxSpA-related rheumatologist visit costs ○ Cost of AxSpA-related rheumatologist visits among all patients • AxSpA-related treatment administration costs ○ Costs associated with AxSpA treatment administration in a medical setting (csDMARDs, advanced treatment (i.e., bDMARDs), NSAIDs, steroid, opioids) • AxSpA-related pharmacy costs ○ Costs of AxSpA-related prescription of medicine (csDMARDs, advanced treatment (i.e., b/tsDMARDs), NSAIDs, steroid, opioids) among all patients • Total costs for AxSpA-related treatment administration and pharmacy costs ○ Sum of AxSpA-related treatment administration costs and AxSpA-related pharmacy costs • AxSpA-related total medical costs ○ Costs of AxSpA-related medical HCRU among all patients. (sum of inpatient, ED, and outpatient costs) • AxSpA-related total costs ○ Cost of AxSpA-related HCRU among all patients. (sum of AxSpA-related inpatient, ED, outpatient, and pharmacy costs) Healthcare costs were adjusted for inflation using the Consumer Price Index for medical components and expressed in 2023 USD.

Table 4. List of Baseline Variables specific to the tsDMARD- / bDMARD-naïve PsA cohort

Variable	Role	Operational definition
Concomitant use of apremilast	Baseline characteristics	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	Specialty visits during the 365 days baseline period were assessed including: • All-cause total rheumatology and dermatology visits ○ Patients with either rheumatology or dermatology visits, N (%)

		○ Number of rheumatology and dermatology visits among all patients • All-cause rheumatology visits ○ Patients with rheumatology visits, N (%) ○ Number of rheumatology visits among all patients • All-cause dermatology visits ○ Patients with dermatology visits, N (%) ○ Number of dermatology visits among all patients

9.4.1. Demographic and Clinical Characteristics

Demographic and clinical characteristics included concomitant medications, history of prior advanced treatments, and healthcare resource utilization measures (Tables 2-4). The SAP (included in Appendix 4) provides greater detail on considered covariates for each cohort, confounders, and operational definitions.

9.4.2. Outcome

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

Effectiveness

A claims-based algorithm was used to assess treatment effectiveness. This algorithm was originally derived and validated for RA using the Veterans Affairs Medicare and pharmacy claims database against low disease activity (LDA; Disease Activity Score [DAS] 28 =< 3.2 units or improvement in DAS 28 >1.2 units measured at the 1-year visit following the index visit.[22] The claims algorithm was used as a proxy for the clinical effectiveness of RA medications. An adapted, but not validated version of this algorithm, was used for this project.

In the original algorithm published, the effectiveness outcome was measured at year 1 using the following six criteria. If all of these six 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
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. Below, in Tables 5 and 6, is the adapted version used in the current study to evaluate comparative effectiveness. The number and proportion of patients satisfying all criteria at month 6 or month 12 post-index were assessed and reported for AxSpA and PsA, respectively:

Table 5. Criteria for the AxSpA Sample

Criteria	Definition
1. High adherence to index treatment.	Proportion of days covered (PDC)≥80% PDC was 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 was 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 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 was 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 initiated other non-index advanced therapy medications during follow-up period (180 days and 365 days). Advanced AxSpA therapy included: tofacitinib, upadacitinib, baricitinib, adalimumab, golimumab, infliximab, etanercept, certolizumab, ixekizumab, secukinumab, deucravacitinib, bimekizumab, brodalumab, tildrakizumab.
3. No dose escalation or increased frequency of the index maintenance dose for advanced therapy.	Dose escalation was assessed by comparing the first observed maintenance dose for the index advanced therapy after loading to all doses observed during the

Criteria	Definition
	remainder of follow-up. If any dose was 20% higher than the index maintenance dose, the patient was flagged as having escalated their dose. Only the index advanced therapy was 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 was used without considering the time window between two administrations.) For patients who only received IV administrations, the number of claims was also calculated. This frequency had to be within 120% of the number expected during 1 year time period based on guidelines. For patients who only received IV administrations, upon sufficient cohort size, a sensitivity analysis, assessing dose escalation based on both the frequency of administration and dosage change was 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 could not initiate therapy with a new conventional DMARD (methotrexate, sulfasalazine, leflunomide) 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 were considered to be used in concomitance with the index advanced treatment and were not considered to be an addition of a new csDMARD.

Criteria	Definition
5. No increase in dose of oral GC compared with baseline.	For patients who received no prescriptions for oral GCs during the 6 months prior to the index date, could not have received more than 30 days of oral GCs 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 GCs in the 6 months prior to the index date, the cumulative GC dose in the 3 months prior to the end of the study period had to 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 GCs in the 6 months prior to the index date, the cumulative GC dose in the 6 months prior to the end of the study period had to be similar (that is, within 120%) to the cumulative dose in the 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 GCs.
6. No more than one GC injection/IV between index date + 90 days and index date + end of follow up (180 days and 365 days after index date), inclusive.	Could not receive GC 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 were considered to be used in concomitance with the index advanced treatment and were not considered to be an addition to a new pain medication.

Criteria	Definition
	Classes include opioids, NSAIDs, non-narcotic analgesics, anticonvulsants, antidepressants, and topical pain medications. Both medical and pharmacy claims were assessed.
8. No use of spinal procedure for AxSpA.	Indicator for claims for spinal procedures at any time during the 6-month and 12-month follow-up periods. This was assessed in medical claims only.

Table 6. Criteria for the bDMARD-naïve PsA Sample

Criteria	Definition
1. High adherence to index treatment.	PDC≥ 80% PDC was 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 values were summed across all claims for the index drug. 2) For medical claims, days' supply was equal to the labelled maintenance frequency: 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 included: tofacitinib, upadacitinib, baricitinib, adalimumab, golimumab, infliximab, etanercept, certolizumab, ixekizumab, secukinumab, ustekinumab, risankizumab or guselkumab, abatacept, apremilast, deucravacitinib, bimekizumab, brodalumab, tildrakizumab.
3. No dose escalation or increased frequency of the index maintenance dose for advanced therapy.	Dose escalation was assessed by comparing the first observed maintenance dose for the index advanced therapy after

Criteria	Definition
	loading to all doses observed during the remainder of follow-up. If any dose is 20% higher than the maintenance index dose, the patient was flagged as having escalated their dose. Only the index advanced therapy was assessed. Dose was calculated as follows: 1) For outpatient Rx claims: Dose = (Strength x (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 was also 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 cohort size, a sensitivity analysis, assessing dose escalation based on both the frequency of administration and dosage change was considered for the subset of patients with available dosage information.
4. No addition of new csDMARD for PsA not already taken during 6 months before or on index date.	Between the index+30 days and end of the study period (at 6 months or 12 months after the index date), patient could not initiate therapy with a new conventional DMARD (methotrexate, sulfasalazine, leflunomide) 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 were considered to be used in concomitance with the index advanced treatment and were not considered to be an addition of a new csDMARD.

Criteria	Definition
5. No increase in dose of oral GC compared with baseline.	For patients who received no prescriptions for oral GCs during the 6 months prior to the index date, could not have received more than 30 days of oral GCs between the index date + 90 days and the end of the study period (6 months or 12 months after the index date), inclusive. Analysis at 6 months: For patients who received prescriptions for oral GCs in the 6 months prior to the index date, the cumulative GC dose in the last 3 months prior to the end of the study period had to 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 GCs in the 6 months prior to the index date, the cumulative GC dose in the 6 months prior to the end of the study period had to 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 GCs.
6. No more than one GC injection/IV between index date + 90 days and index date + end of follow up (180 days and 365 days after index date), inclusive.	Could not have received GC 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 were considered to be used in concomitance with the index advanced treatment and will not be

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

Outcome variables that were assessed
The number and proportion of patients that satisfy the effectiveness criteria.

Primary Outcome:
- Patients that satisfy all 8 effectiveness criteria

Secondary Outcome:
- Patients that satisfy each of the effectiveness criteria

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

Persistence
Persistence on index therapy within 12 months of treatment initiation was assessed. Persistence, defined as “duration of time from initiation to discontinuation of the index therapy”, was estimated (in months). Patients were 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 was imputed according to the labelled maintenance frequency:
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 months and 12 months of index treatment initiation were assessed as per patient per month (PPPM). The AxSpA-related HCRU and costs were considered 'AxSpA-related' if the visit claim was associated with a record of a diagnosis of AxSpA.

HCRU

- All-cause:
  - Number of rheumatologist visits during follow-up
  - Number of inpatient admissions during follow-up
  - Length of all-cause inpatient admissions (days) during follow-up
  - Number of emergency department (ED) visits during follow-up
  - Number of outpatient visits during follow-up
  - Number of prescription fills during follow-up

- AxSpA-related:
  - Number of AxSpA-related rheumatologist visits during follow-up
  - Number of AxSpA-related inpatient admissions during follow-up
  - Length of AxSpA-related inpatient admissions (days) during follow-up
  - Number of AxSpA-related ED visits during follow-up
  - Number of AxSpA-related outpatient visits during follow-up
  - Number of AxSpA-related prescription fills during follow-up

Costs

All costs were adjusted to 2023 US dollars using Annual CPI-U (Bureau of Labor Statistics Series ID: CUUR0000SAM), Medical care in US city average, all urban consumers.

- All-cause:
  - Inpatient costs during follow-up
  - Rheumatology visit costs during follow-up
  - ED costs during follow-up
  - Outpatient costs during follow-up
  - Pharmacy costs during follow-up
  - Total medical costs (inpatient + ED + outpatient) during follow-up
  - Total costs (total medical + pharmacy) during follow-up

- AxSpA-related:
  - AxSpA-related inpatient costs during follow-up
  - AxSpA-related rheumatology visit costs during follow-up
  - AxSpA-related ED costs during follow-up
  - AxSpA-related outpatient costs during follow-up

- AxSpA-related treatment administration costs (ED and outpatient claims) during follow-up (associated with AxSpA treatment administration in a medical setting i.e., csDMARDs, advanced treatment [i.e., bDMARDs], NSAIDs, steroid, opioids)
- AxSpA-related pharmacy costs (pharmacy claims for AxSpA-related treatment) during follow-up
- AxSpA-related treatment administration and pharmacy costs during follow-up
- AxSpA-related total medical costs (inpatient + ED + outpatient) during follow-up
- AxSpA-related total costs (total AxSpA-related medical + AxSpA-related treatment administration and pharmacy) during follow-up

Considering adverse events (AEs) and adverse reactions, it should be noted that in these data sources, individual patient data were not retrieved or validated, and it was not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) were not met.

9.5. Data Sources and Measurement

All variables for the study are derived from the Komodo Healthcare Map dataset. Identification of disease populations, safety outcomes of interest, and drugs prescribed were implemented using International Classification of Diseases – Tenth Revision (ICD-10) codes, current procedure terminology (CPT) procedure codes, and prescribing data (e.g., NDC) in the patients' records. Specific codes for exposure, outcomes and covariates are outlined in the SAP.

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 US. In the Komodo's Healthcare Map database, diagnoses, procedures, and prescription drugs are coded using ICD-9/10-CM, CPT-4, HCPCS, and NDC codes.

9.6. Bias

Given the nature of claims data and the treatment landscape of advanced therapies in rheumatologic diseases, biases may exist due to confounding by indication.[24] For example, as JAKi are approved in the US only in patients with inadequate response or intolerance to TNFi, patients included in the tofacitinib cohort might be more severe and previously exposed to a greater number of advanced medications. To minimize this, propensity score (PS) weighting was utilized to adjust for measured confounding factors; however, residual confounding from unmeasured factors, or factors measured with error in claims data cannot be excluded. The study included only patients who have at least 6 months or 12 months of continuous enrollment after index date to ensure there is sufficient time to assess the study outcomes. This criterion may have introduced selection bias toward patients with less severe disease, as patients who did not meet the enrollment criteria, for reasons such as death or loss of health care coverage, would have been excluded.[25] The extent to which selection bias was present was not specifically examined in this study. Additionally, since this is a claims analysis, misclassification and measurement bias due to the limited nature of the variables

collected was possible in the analysis.[26] Sensitivity analyses were conducted when appropriate to address misclassification (see Section 9.9.4).

9.7. Study Size

A preliminary feasibility analysis for the PsA bDMARD naïve cohort indicated a sample size range of approximately 600 patients on tofacitinib who were bDMARD naïve, 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.

An additional preliminary feasibility analysis for the AxSpA cohort indicated a sample size range of approximately 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.

These sample sizes were deemed adequate to proceed with statistical analyses, allowing for the fit (analytic stability and interpretability) of the planned models (e.g., PS-weighted comparisons, time-to-event analyses). The sample sizes were along the continuum with those of published literature[21-23] and methodological guidance for observational studies,[27] and were sufficient to support the planned statistical analyses, including comparative effectiveness and persistence outcomes. Additionally, the continuous enrollment of patients ensured follow-up time for endpoint assessment in the evaluation of study objectives.

9.8. Data Transformation

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the SAP, which is dated, filed and maintained by the sponsor (Appendix 4). R version 4.4.2 was used to conduct the analyses.

Briefly, data transformations were used to construct categorical variables, exposure categories based on mechanism of action (e.g. TNFi), and composite outcomes (e.g. treatment effectiveness criteria), as outlined in the SAP.

9.9. Statistical Methods

Statistical methods are documented in the SAP (Appendix 4) and briefly described below.

9.9.1. Main Summary Measures

For demographic and clinical characteristics, continuous variables were summarized by mean (standard deviation, SD), median, and quartile (Q1, Q3). Categorical variables were summarized by count and percentage for each category.

PSs were estimated using a multinomial logistic regression model to account for multiple treatment cohorts. Average Treatment Effect among the Treated (ATT) weights were generated using odds-based (Standardized Mortality Ratio, SMR) weighting. The covariates included in the PS model were selected based on statistical considerations and clinical judgment.

For the AxSpA sample, the same patient could contribute multiple observations if they initiated or switched to another advanced therapy during the index identification period. Each index date generated a separate episode with its own baseline covariates and corresponding PS estimate. Separate PS models were independently fit for each sample (AxSpA and b/tsDMARD-naïve PsA) with corresponding follow-up window. Covariate balance was assessed before and after weighting using standardized mean differences (SMDs). Covariates remain unbalanced after weighting were included in the outcome model to further reduce confounding.

Patients were followed from index date (inclusively) up to the earliest of 6 months or 12 months after index date (depending on the analysis) or switch to/initiation of another advanced medication (other than the index medication). A robust (sandwich) variance estimator was applied in all AxSpA outcome analyses to account for within patient correlation, as multiple samples may exist for the same patient.

9.9.2 Main Statistical Methods

Treatment Effectiveness

The analysis of the primary objective evaluated treatment effectiveness during the 6-month follow-up period, defined as time to the first failure of any effectiveness criterion. Secondary analyses applied the same methodology to the 12-month follow-up window. Risk of effectiveness-criterion failure was compared across treatment cohorts using Cox proportional hazards models in both the AxSpA and PsA samples.

Both unweighted and PS-weighted analyses were conducted. Unadjusted and adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were estimated. In addition to the composite endpoint, counts and proportions of patients failing each individual effectiveness criterion were descriptively summarized, including characterization of the first criterion not met.

Persistence

Persistence on index therapy within 12 months after index treatment initiation was evaluated, Cox proportional hazards models were used to compare the index medication classes (TNFi or IL-17i) vs. tofacitinib. Survival curves derived from the Cox model were used to estimate the median duration of index treatment.

HCRU and Costs (AxSpA Sample Only)

For the AxSpA sample, HCRU outcomes were assessed using generalized linear models (GLMs) or two-part models, as appropriate, to account for zero-inflated utilization measures. All-cause and AxSpA-related healthcare costs were evaluated separately for the 6-month and 12-month follow-up periods.

9.9.2. Missing Values

No imputation for missing values was performed, besides imputation for days of supply for injectable medications and pharmacy claims with missing days of supply. Counts and percentages of missing values were presented in the tables where applicable. For example, it was acceptable for the patients with "unknown / missing" baseline data to be removed from the analysis at the time of generating PS scores.

9.9.3. Sensitivity Analyses

Five sensitivity analyses were conducted, each based on modifications (applied one at a time) to derive new definitions of "all effectiveness criteria met."

a. Excluding criterion 1 (high adherence) to avoid bias estimating adherence of drugs with different administration routes using health claims data.
b. Excluding 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. Criterion 5 was updated to use a cutoff of 50% (instead of 20%) to identify increase in dose of oral GC.
d. Excluding criterion 5 due to shorter time for outcome measure for the analyses at 6 months.
e. Criterion 3: For patients who only received IV administrations, a sensitivity analysis, assessing dose escalation based on both the frequency of administration and dosage change was completed for the subset of patients with available dosage information.

9.9.4. Amendments to the Statistical Analysis Plan

Amendment SAP v2.3

The change indicated in the first and second rows was motivated by a failure of software to run. Hence no final analyses influenced this amendment. This change was intended to be made with Amendment 2.2. The third-row entry was meant to give the programmers flexibility in the way the results are displayed; the intent in the use of the Hazard Ratio (HR) remains. The fourth-row entry was meant to correct the link (should have been log link, not inverse link) and text was added to give the programmers some leeway in determining the best distribution. As such, no final analyses influenced this set of changes:

FROM:	TO:	Rationale for change
Section 4.7.4.1 AxSpA *Treatment effectiveness 3rd paragraph* If the Cox PH frailty model is not feasible (e.g., the algorithm fails to converge), an acceptable alternative model is logistic regression, in which the composite outcome of "All Effectiveness Criteria Met" (yes/no) is assessed at 180 and 365 days, applying GEE to account for within-patient correlation, otherwise correspondingly specified. Treatment group comparison to tofacitinib will be estimated via Odds Ratio, along with p-value and 95%CIs.	Section 4.7.4.1 AxSpA *Treatment effectiveness* *3rd and 4th paragraphs* If the Cox PH frailty model is not feasible (e.g., the algorithm fails to converge), an acceptable alternative model is to use robust (sandwich) variance estimator in the Cox PH model to account for within patient correlation. If there is still algorithmic failures or lack of feasibility, a second acceptable alternative model is logistic regression, in which the composite outcome of "All Effectiveness Criteria Met" (yes/no) is assessed at 180 and 365 days, applying GEE to account for within patient correlation, otherwise correspondingly specified. Treatment group comparison to tofacitinib will be estimated via Odds Ratio, along with p-value and 95%CIs.	We encountered an issue with using both frailty and weight statement in the Cox model. The software being used (coxph()), doesn't support observation-level weights in the penalized partial likelihood used to fit frailties. An alternative found to work and keep the frailty model was to use the software's "robust sandwich SEs using cluster option."
Section 4.7.4.1 AxSpA *Persistence 2nd paragraph*	Section 4.7.4.1 AxSpA *Persistence 2nd and 3rd paragraphs* If the Cox PH frailty model is not feasible (e.g., the algorithm fails to	

FROM:	TO:	Rationale for change
If the Cox PH frailty model is not feasible (e.g., the algorithm fails to converge), an acceptable alternative model is logistic regression, applying GEE to account for within-patient correlation, otherwise, correspondingly specified. Treatment group comparison to tofacitinib will be estimated via Odds Ratio, along with p-value and 95%CIs.	converge), an acceptable alternative model is to use robust (sandwich) variance estimator in the Cox PH model to account for within patient correlation. If there is still algorithmic failures or lack of feasibility, a second acceptable alternative model is logistic regression, in which the persistence (yes/no) is assessed at 365 days, applying GEE to account for within-patient correlation, otherwise correspondingly specified. Treatment group comparison to tofacitinib will be estimated via Odds Ratio, along with p-value and 95%CIs.	
Applies to Sections 4.7.3.1, 4.7.3.2, 4.7.4.1, 4.7.4.2: A HR >1 will be interpreted as a higher likelihood of treatment effectiveness in patients who initiated tofacitinib versus the comparator cohort.	Applies to Sections 4.7.3.1, 4.7.3.2, 4.7.4.1, 4.7.4.2: The HR will be used to compare effectiveness (or effectiveness not achieved) in comparator versus tofacitinib.	To allow programmers the flexibility to express the HR, whether >1 or <1
Section 4.7.4.1 *HCRU and costs* ⋯Mean cost PPPM will be reported for both the unweighted and weighted cohorts. • The amount of "zero dollars" present for a dollar-cost variable will be determined. If the rate of zero dollars is less than 10%, each $0 observation will be imputed with $1. A gamma GLM using the inverse link will be applied. • If the rate of zero dollars is at least 10%, two-part models will be applied. The first part will be a probit model to estimate the probability of $0, with the second part being a gamma GLM using the inverse link.	Section 4.7.4.1 *HCRU and costs* ⋯ Mean cost PPPM will be reported for both the unweighted and weighted cohorts. Data will be examined to inform which is the best distribution to be applied (e.g., Poisson, zero-inflated Poisson, negative binomial), and their corresponding links will be used. It is likely that the gamma will be chosen. If so: • The amount of "zero dollars" present for a dollar-cost variable will be determined. If the rate of zero dollars is less than 10%, each $0 observation will be imputed with $1. A gamma GLM using the log link will be applied. • If the rate of zero dollars is at least 10%, two-part models will be applied. The first part will be a probit model to estimate the probability of $0, with the second part being a gamma GLM using the log link.	To correct the specified link (log link, not inverse link) and to give the programmers some leeway in determining the best distribution.

Amendment: SAP v2.2

This change was motivated by a failure of software to run. Hence no final analyses influenced this amendment.

Changes in text from v2.1 to v2.2:

FROM:	TO:	Rationale for change
Section 4.7.3.1 AxSpA *Treatment effectiveness* *3rd paragraph* If the Cox PH frailty model is not feasible (e.g., the algorithm fails to converge), an acceptable alternative model is logistic regression, in which the composite outcome of "All Effectiveness Criteria Met" (yes/no) is	Section 4.7.3.1 AxSpA *Treatment effectiveness* *3rd and 4th paragraph* If the Cox PH frailty model is not feasible (e.g., the algorithm fails to converge), an acceptable alternative model is to use robust (sandwich) variance estimator in the Cox PH model to account for within patient correlation.	We encountered an issue with using both frailty and weight statement in the Cox model. The software being used (coxph()), doesn't support observation-level weights in the penalized partial likelihood used to fit frailties. An alternative found to work and keep the

FROM:	TO:	Rationale for change
assessed at 180 and 365 days, applying GEE to account for within patient correlation, otherwise correspondingly specified. Treatment group comparison to tofacitinib will be estimated via Odds Ratio, along with p-value and 95%CIs.	If there is still algorithmic failures or lack of feasibility, a second acceptable alternative model is logistic regression, in which the composite outcome of "All Effectiveness Criteria Met" (yes/no) is assessed at 180 and 365 days, applying GEE to account for within-patient correlation, otherwise correspondingly specified. Treatment group comparison to tofacitinib will be estimated via Odds Ratio, along with p-value and 95%CIs.	frailty model was to use the software's "robust sandwich Ses using cluster option."

Amendment: SAP v2.1

The set of items noted in this amendment were initiated to add clarifications or correct the SAP text itself. None of the analyses influenced the first 3 items in this amendment. Please see the third row in the table below. None of the final analyses influenced that item in this amendment.

Changes in text from v2.0 to v2.1:

FROM:	TO:	Rationale for change
Not in SAP	Added as Appendix C	[redacted] requires a change log and an area to document decisions within the SAP itself. The change log had not been previously added.
6.3 Appendix B header	Delete 6.3 Appendix B header and renumber from that point	Removing redundant header
Table 1 entry: "Concomitant use of steroid with index medication during the baseline period"	Table 1 entry: "Concomitant use of steroids with index medication"	Clarify the name of the variable
Section 4.6 Missing Data "When missing data occur, no imputation will be made – with the exception of imputation for days of supply for injectable medications (see variables and outcome section). All statistics will be calculated with nonmissing values. Counts and percentages of missing values will be presented in the tables where applicable."	Section 4.6 Missing Data "When missing data occur, no imputation will be made – with the exception of imputation for days of supply for injectable medications and pharmacy claims with missing days of supply (see variables and outcome section). All statistics will be calculated with non-missing values. Counts and percentages of missing values will be presented in the tables where applicable. For example, it is acceptable for the patients with 'unknown / missing' baseline data be removed from the analysis at the time of generating PS scores."	Clarify how missing data will be handled with respect to PS generation. This item should have been added into SAP v2.0 and is being added now. As such the statement below regarding SAP v2.0 applies, that is, this change was not influenced by the final analyses.

Decisions post v2.0:

Section 4.7.3.1 AxSpA, *Propensity Scores*: The text of the SAP asked that the GEE methodology be tested for feasibility; if it was not feasible, use the fixed-effect multinomial model instead. The GEE method was found not to be feasible. Work using PSs for AxSpA proceeded using the multinomial model with fixed effects only.

Amendment: SAP v2.0

The set of items noted in this amendment were initiated to clarify the instructions (e.g., clarify definitions of variables) for the programmers. These items arose while initial analyses were being performed, in discussion with the programmers, specifically in preparation of the propensity-score estimation. In that sense, the analyses performed did influence some of these changes noted in the items.

All changes/clarifications described below were included in the SAP amendment before any analyses using the below were conducted. Hence, there were no analyses performed, hence none of the analyses influenced the items in this amendment.

Changes in text from v1.0 to v2.0:

FROM:	**TO:**	**Rationale for change**
Table 1:	Added entries "Concomitant use of steroids with index medication during the baseline period" "Recent use of csDMARD"	Add variables as per clinical judgment that they should be included for completeness
Table 1 entry "Concomitant use of csDMARD with index medication during the baseline period"	Table 1 entry: "Concomitant use of csDMARD with index medication"	Clarify the name of the variable
Table 4 entry 1 Table 4 entry 3 "along with a diagnosis of PsA/PsO"	Table 4 entry 1 Table 4 entry 3 "along with a diagnosis of AxSpA"	Corrected a typographical error
Table 4 Entry 7 "No use of pain medication class not observed during baseline period or at index."	Table 4 Entry 7 "No use of pain medication class not observed during the 6-months baseline period or at index."	Clarify the name and definition of the variable
Table 4 Entry 7 "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 the pre-index period or used as a concomitant medication with the index treatment." … "For opioid, for people already on a strong opioid at baseline (which is all opioids except tramadol and codeine), failure will be identified as a claim/administration for a new strong opioid (not use at baseline). For those on a weak opioid (tramadol/codeine), failure will be identified as a claim/administration for a new weak opioid (not use at baseline), or a new strong opioid. For those not on any opioids at baseline, any new opioid prescription/administration will be considered as a failure." "For other drug classes, use of a new pain medication class (not used at baseline) will be identified as a failure."	Table 4 Entry 7 "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 the 6 months before the index date or used as a concomitant medication with the index treatment." … "For opioid, for people already on a strong opioid during the 6 months prior to the index date (which is all opioids except tramadol and codeine), failure will be identified as a claim/administration for a new strong opioid (not use at baseline). For those on a weak opioid during the 6 months prior to index date (tramadol/codeine), failure will be identified as a claim/administration for a new weak opioid (not use during the 6 months prior to the index date), or a new strong opioid. For those not on any opioids during the 6 months prior to the index date, any new opioid prescription/administration will be considered as a failure." "For other drug classes, use of a new pain medication class will be identified as a failure."	Clarify the definition of the variable
Table 5 Entry 4: "No addition of new csDMARD for	Table 5 Entry 4:	Clarify the name and definition of the variable

FROM:	TO:	Rationale for change
PsA not already taken during baseline period or at index."	"No addition of new csDMARD for PsA not already taken during the 6-month baseline period or at index."	
Table 5 Entry 7: "No use of new topical treatment, actinotherapy or oral retinoid (class level) not observed during the baseline period or at index"	Table 5 Entry 7: "No use of new topical treatment, actinotherapy or oral retinoid (class level) not observed during the 6 months baseline period or at index"	Clarify the name and definition of the variable
Table 5 Entry 7: "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." … For topical steroids, the following rules will apply. For those not on any topical steroids at baseline, any new topical steroid prescription will be considered as a failure. For those already on topical steroids at baseline, failure will be identified as (1) either a new medication which is considered to be more potent that the medication used at baseline (see Appendix Table 13) or (2) as a new medication that is in the same potency class as the medication used during the 6 months prior to the index date. For other drug classes, use of a new drug class (not observed at baseline) will be identified as a failure.	Table 5 Entry 7: "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 (i.e., 6 months before the index date) or used as a concomitant medication with the index treatment." … For topical steroids, the following rules will apply. For those not on any topical steroids during the 6 months prior to the index date, any new topical steroid prescription will be considered as a failure. For those already on topical steroids during the 6 months prior to the index date, failure will be identified as (1) either a new medication which is considered to be more potent that the medication used during the 6 months prior to the index date (see Appendix Table 13) or (2) as a new medication that is in the same potency class as the medication used during the 6 months prior to the index date. For other drug classes, use of a new drug class will be identified as a failure.	Clarify the name and definition of the variable
Table 5 Entry 8: "No use of pain medication class not observed during baseline period or at index."	Table 5 Entry 8: "No use of pain medication class not observed during the 6-month baseline period or at index."	Clarify the name of the variable
Table 5 Entry 8: "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." … "For opioids, for people already on a strong opioid at baseline (which is all opioids except tramadol and codeine), failure will be identified as a claim/administration for a new strong opioid (not use at baseline). For those on a weak opioid at baseline (tramadol/codeine), failure will be identified as a claim/administration for a new weak opioid (not use at baseline), or a new strong opioid. For those not on any opioids at baseline, any new	Table 5 Entry 8: "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 (6 months before index date) or used as a concomitant medication with the index treatment." … "For opioids, for people already on a strong opioid during the 6 months prior to the index date (which is all opioids except tramadol and codeine), failure will be identified as a claim/administration for a new strong opioid (not use during the 6 months prior to the index date). For those on a weak opioid during the 6 months prior to the index date (tramadol/codeine), failure	Clarify the name of the variable

FROM:	TO:	Rationale for change
opioid prescription/administration will be considered as a failure. For other drug classes (other than opioids), use of a new pain medication class will be identified as a failure."	will be identified as a claim/administration for a new weak opioid (not use during the 6 months prior to the index date), or a new strong opioid. For those not on any opioids during the 6 months prior to the index date, any new opioid prescription/administration will be considered as a failure. For other drug classes (other than opioids), use of a new pain medication class will be identified as a failure."	
Section 4.7.3.1 AxSpA *Propensity Scores* "PS will be generated. The preferred methods are below; the method most feasible will be utilized." 1. "Multinomial logistic regression will be used to model a dependent variable with three categories representing the treatment groups (IL-17i, anti-TNFi, tofacitinib). Generalized Estimating Equations (GEE) will account for within-patient correlation due to multiple time segments from the same patient. The probability of each treatment will be estimated based on the model and used as the propensity score." … "Logistic Regression, with generalized estimating equations for the repeated measures and the logit link as in 1) above, predicting two treatment groups in each comparison namely IL-17i versus tofacitinib, and then again anti-TNFi versus tofacitinib; that is, fit two separate models."	Section 4.7.3.1 AxSpA *Propensity Scores* "PS will be generated. The preferred methods are below; the method most feasible will be utilized." 2. "Multinomial logistic regression will be used to model a dependent variable with three categories representing the treatment groups (IL-17i, anti-TNFi, tofacitinib). If feasible, the model will incorporate Generalized Estimating Equations (GEE) to account for within-patient correlation due to multiple time segments from the same patient; otherwise, the model will only have fixed effects. The probability of each treatment will be estimated based on the model and used as the propensity score." … 3. "Logistic Regression with optional generalized estimating equations for the repeated measures, otherwise model will only have fixed effects, as in 1) above), predicting two treatment groups in each comparison namely IL-17i versus tofacitinib, and then again anti-TNFi versus tofacitinib; that is, fit two separate models using a logit link for each."	Acknowledge that GEE methodology may not be feasible, and that fixed effects PS most likely extremely similar to GEE-derived ones.
Section 4.7.3.1 AxSpA *PS weighting Methodology* "Weighting by odds (that is, the Standardized Mortality Ratio weight, SMR) will be used to control for confounders when comparing outcomes between treatment cohorts. We will conduct standard diagnostics comparing standardized mean differences for each confounding variable between the treatment cohorts before and after weighting. Variables with standardized mean differences	Section 4.7.3.1 AxSpA *PS weighting Methodology* "Weighting by odds (that is, the Standardized Mortality Ratio weight, SMR) will be used to control for confounders when comparing outcomes between treatment cohorts. We will conduct standard diagnostics comparing standardized mean differences for each confounding variable between the treatment cohorts before and after weighting. Variables with	To acknowledge that clinical input is needed and will be utilized.

FROM:	TO:	Rationale for change
(SMD) >=0.1 after weighting will be included as terms in the outcome regression models. This aims to make treatment status independent of the measured confounders at baseline. Variables incorporated into the weighting may be reassessed if not successfully implemented (e.g., model fails to converge). No trimming will be applied."	standardized mean differences (SMD) >=0.1 after weighting will be included as terms in the outcome regression models. This aims to make treatment status independent of the measured confounders at baseline. Variables incorporated into the weighting may be reassessed if not successfully implemented (e.g., model fails to converge). No trimming will be applied. Clinical judgment may also be utilized in the final decision of including or excluding variables, for example, to avoid duplicative variables containing the same information."	
Section 4.7.3.2 PsA *PS weighting Methodology* "Weighting by odds (that is, the Standardized Mortality Ratio weight, SMR) will be used to control for confounders when comparing outcomes between treatment cohorts. We will conduct standard diagnostics comparing standardized mean differences for each confounding variable between the treatment cohorts before and after weighting. Variables with SMDs >=0.1 after weighting will be included as terms in the outcome regression models. This aims to make treatment status independent of the measured confounders at baseline. Variables incorporated into the weighting may be reassessed if not successfully implemented (e.g., model fails to converge). No trimming will be applied."	Section 4.7.3.2 PsA *PS weighting Methodology* "Weighting by odds (that is, the Standardized Mortality Ratio weight, SMR) will be used to control for confounders when comparing outcomes between treatment cohorts. We will conduct standard diagnostics comparing standardized mean differences for each confounding variable between the treatment cohorts before and after weighting. Variables with SMDs >=0.1 after weighting will be included as terms in the outcome regression models. This aims to make treatment status independent of the measured confounders at baseline. Variables incorporated into the weighting may be reassessed if not successfully implemented (e.g., model fails to converge). No trimming will be applied. Clinical judgment may also be utilized in the final decision of including or excluding variables, for example, to avoid duplicative variables containing the same information."	To acknowledge that clinical input is needed and will be utilized.
Not in SAP v1.0	Appendix B "The detailed list of procedures, HCPCs, NDC and ICD-10 codes are listed in a stand-alone Excel workbook"	Note the existence of workbook
Not in SAP v1.0	Appendix B Table 8b. Phototherapy procedures Added entries "6A600ZZ" and "6A601ZZ"	Add for completeness

FROM:

Figure 9. Study Diagram for AxSpA and PsA Samples – 6 Months Follow up Period*

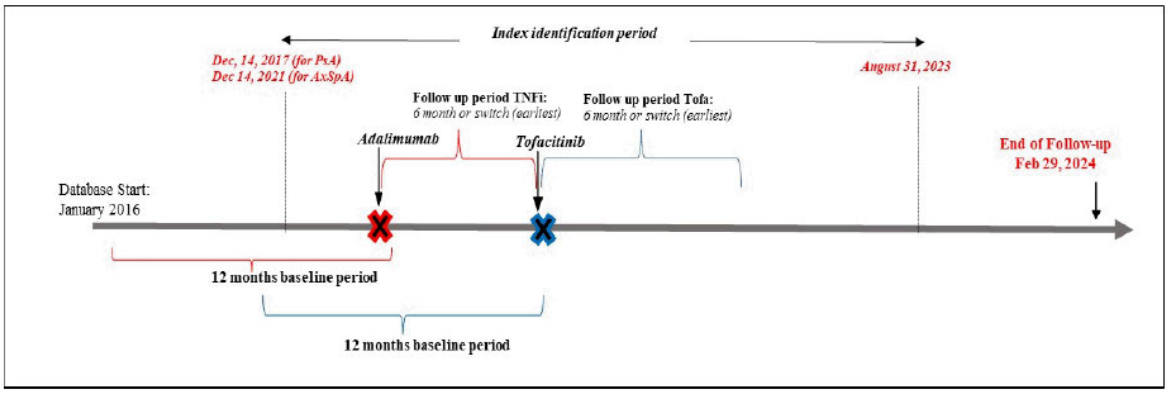
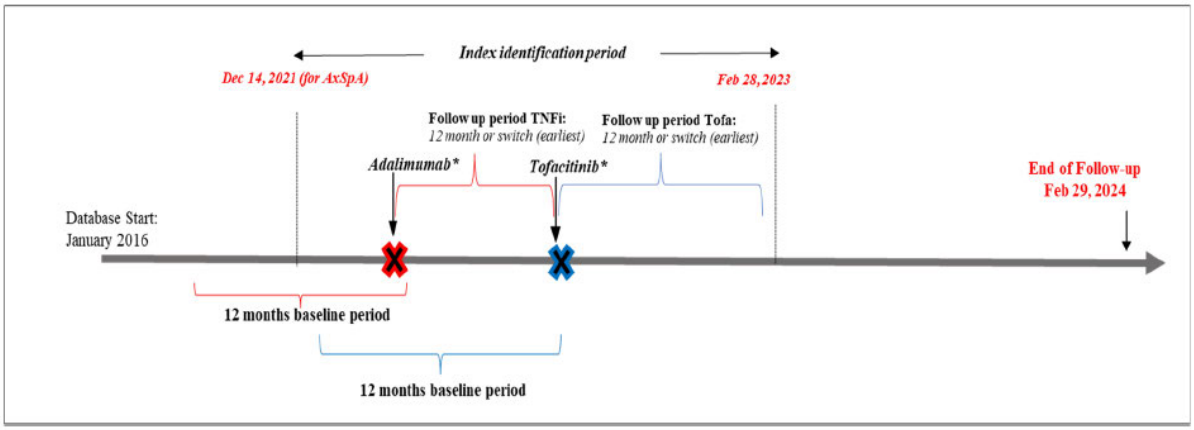
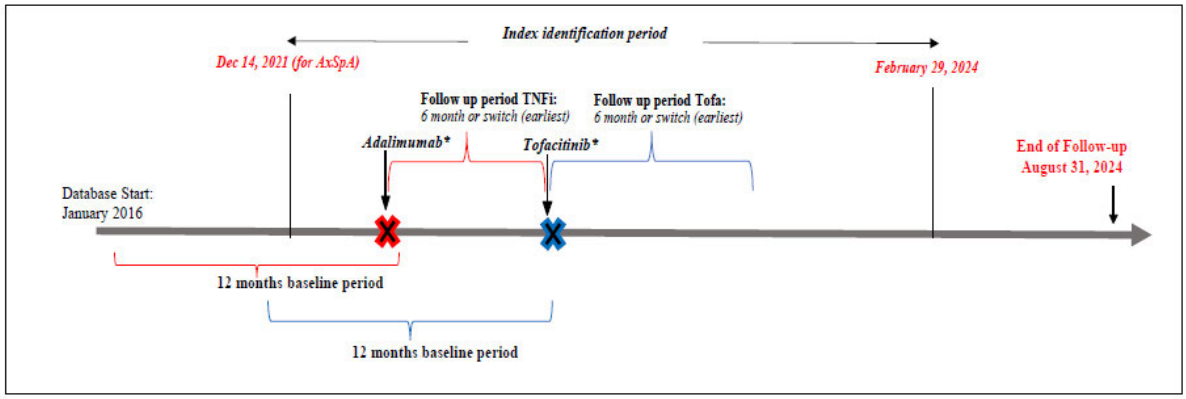


Figure 10. Study Diagram for AxSpA and PsA Samples – 12 Months Follow up Period*



TO:

Figure 11a. 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 12b. Study Diagram for PsA b/tsDMARD-naive patients – 6 Months Follow up Period

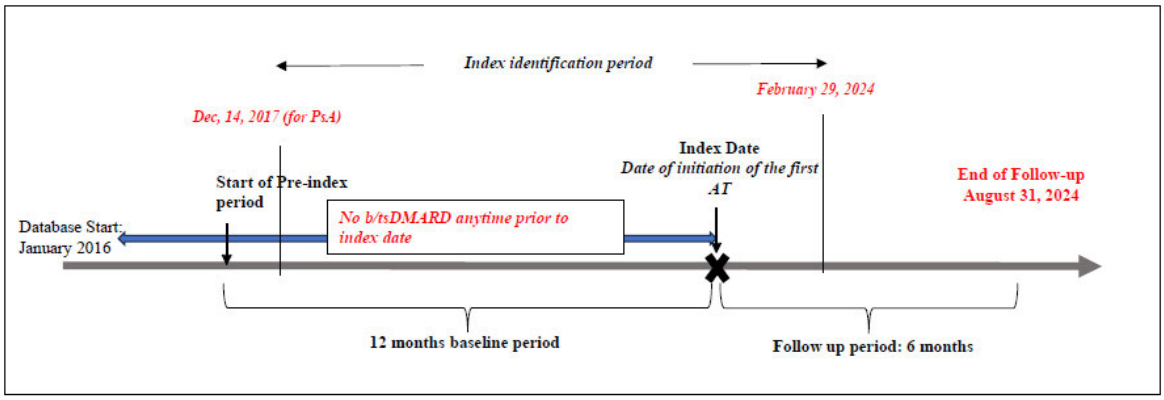
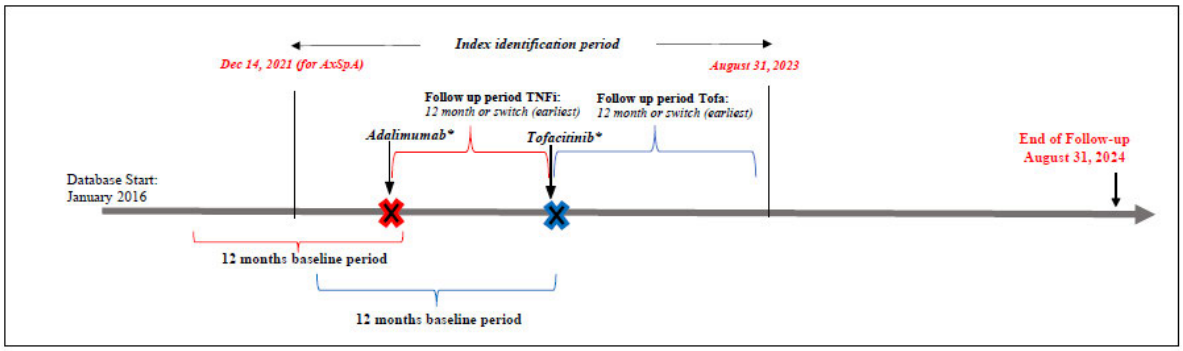
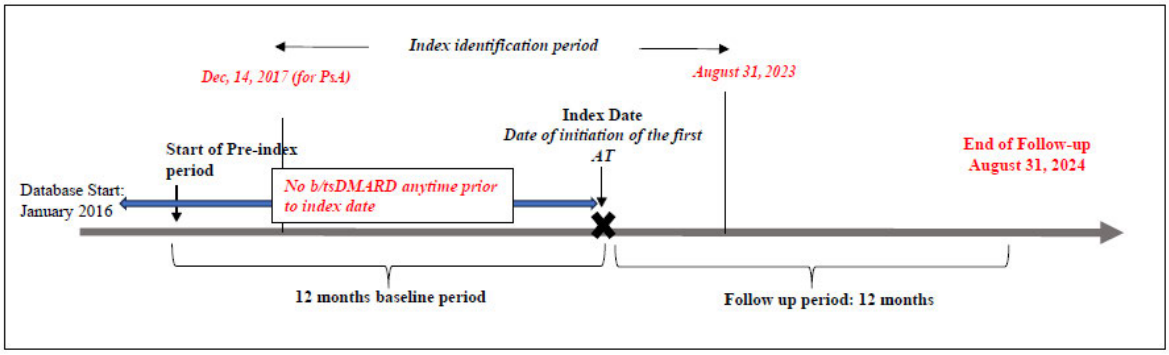


Figure 13a. Study Diagram for AxSpA– 12 Months Follow up Period



**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 14b.Study Diagram for PsA b/tsDMARD-naive patients – 12 Months Follow up Period



RATIONALE: Clarify applicable dates; call out specific differences between PsA and AxSpa sets. At the time the greenlight was given to the vendor to start the analyses, more data were available in the databases (COHORT_1233283) expanding the end of the follow up and as a consequence the index identification window. A statement was already included in the protocol and SAP to cover this possibility under the study design section "*For illustration purposes, the calendar axis may not be proportional. The end of the follow up may be expanded if more recent data are available at the time of study start." The figures were updated in the SAP for clarity as an SAP amendment was necessary to cover other changes. Note: Figures replaced in both body of text and in the abstract.

9.10. Quality Control

The study team adhered to the highest quality of scientific rigor and aimed to generate accurate, quality results. The quality control (QC) process included, but was not limited to the following procedures:

The study design and clinical contextualization were informed and reviewed by a clinical expert who previously derived and validated an administrative claims-based algorithm for the effectiveness of medications in rheumatologic conditions.[22] Additionally, this clinical expert provided background on the disease state, advised on appropriate patient cohort criteria, and

reviewed and validated codes to identify relevant comorbidities, procedures, and treatments among individuals selected for inclusion in this study.

In partnership with this clinical expert and Genesis Research Group, the Pfizer team developed a detailed study protocol that included patient cohort definitions, variables, codes, and a statistical analysis plan in accordance with Pfizer's standard operating procedures. Both the study protocol and SAP provided opportunities to incorporate additional feedback on the approach and address any potential gaps.

To generate the most accurate dataset for analysis, Genesis Research Group incorporated quality assurance checks throughout the study execution process, which may have included individual-level record/element review, independent double programming, and an additional internal medical code review of all code lists used.
The analysis was conducted by data scientists and/or analysts under the supervision of the lead researcher, pharmacoepidemiologist, and biostatistician. All intermediate and final outputs were reviewed by the full study team to ensure accuracy.

For any modeling, the variable distributions, model assumptions, and model fit were reviewed and evaluated by the study team. If needed, Genesis Research Group's research team reviewed previously published literature and/or internally conducted analyses to further validate the results.

Results were reviewed by the Pfizer cross-functional team, including members of Statistics, Medical Affairs, and Real-World Evidence and Epidemiology, to ensure that they met Pfizer's expectations.

9.11. Protection of Human Subjects

Subject information and consent
Not applicable.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)
This study is a retrospective, non-interventional study that used 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.

Ethical conduct of the study
The study was 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.[28,29]

10. RESULTS
The full set of results can be found in the deliverable in Appendix 7.

10.1. Participants

10.1.1. AxSpA Sample

The database included a total of 2,252,390 patients with evidence of ≥1 inpatient or ≥2 outpatient claims (>30 days apart) with a diagnosis code for AxSpA in the Komodo Healthcare Map database between January 1, 2016 and August 31, 2024. After applying all of the inclusion and exclusion criteria for the 6-month follow up cohort, 17,846 patients were selected for the analysis, with 829, 14,056, and 4,472 patients in the tofacitinib, TNFi, and IL-17i cohorts, respectively. 12,549 patients remained in the 12-month follow up cohort, with 586, 9,885, and 2,933 patients in the tofacitinib, TNFi, and IL-17i cohorts, respectively. The attrition tables for the AxSpA 6-month and 12-month follow up cohorts are available the Study Results Workbook (Table 1a/1b).

10.1.2. PsA Sample

The database included a total of 602,801 patients with evidence of ≥1 inpatient or ≥2 outpatient claims (>30 days apart) with a diagnosis code for PsA in the Komodo Healthcare Map database between January 1, 2016 and August 31, 2024. After applying all of the inclusion and exclusion criteria for the 6-month follow up cohort, 34,817 patients were selected for the analysis, with 765, 28,033, and 6,019 patients in the tofacitinib, TNFi, and IL-17i cohorts, respectively. 29,154 patients remained in the 12-month follow up cohort, with 684, 23,518, and 4,952 patients in the tofacitinib, TNFi, and IL-17i cohorts, respectively. The attrition tables are available in the Study Results Workbook (Table 1c/1d)

10.2. Descriptive Data

10.2.1. AxSpA 6-month Follow-up Population

Mean age at index ranged from 47.1–48.1 years, while the proportion of female patients ranged from 65.0–69.2%. In the pre-index period, 60.2% of patients who received tofacitinib had used ≥2 prior ATs vs. 14.0% for the TNFi cohort and 39.8% for the IL-17i cohort. Prior to PS weighting, use of steroids, opioids, non-opioid pain medications, and csDMARDs at baseline was higher in the tofacitinib cohort vs. the TNFi and IL-17i cohorts. In the post-weighting tofacitinib cohort, the median age was 49 years [interquartile range (IQR) 38–57], with 70% of patient being female. In both the post-weighting TNFi and the IL-17i cohorts, the median age was 49 years [IQR 39–57], with 71% of patient being female. Across all treatment cohorts, the SMD for most features was <0.10. Before PS weighting, most demographics and baseline characteristics were imbalanced (SMDs >0.1). Excluding HCRU and costs, the biggest SMDs for the tofacitinib vs. TNFi cohort and tofacitinib vs. IL-17i cohort were noted for the 'number of distinct advanced medications in pre-index history' (SMD 1.5) and 'number of distinct IL-17s in pre-index history' (SMD 0.68), respectively. After PS weighting, demographics and baseline characteristics were generally well balanced (SMDs <0.1). Features where SMD >0.10 for both the tofacitinib vs. TNFi and the tofacitinib vs. IL-17i include pre-index history of advanced medications by medication, number of distinct JAKi/TNFi/non-TNFi in pre-index history, and number of distinct IL-17s in pre-index history (tofacitinib vs. IL-17i cohort only). These features were not additionally adjusted for in the 6-month treatment failure, or the 6-month HCRU and costs analyses. Serious infection (92–93%), mood/mental disorders (69–73%), cardiovascular disease (67–72%), and osteoarthritis (68–71%) were the most prevalent comorbid conditions pre-index. A small proportion of patients within the treatment cohorts had incomplete demographic information at index (tofacitinib: N=14 (1.7%), TNFi: N=213 (1.5%), and IL-17i: N=64 (1.4%)). The post-weighting results exclude patients with unknown sex, other only combined insurance, and/or unknown

region at index. The demographic tables may be seen in the Study Results Workbook (Table 2a).

10.2.2. AxSpA 12-month Follow-up Population

In total, 12,549 new starts of treatment were included in the analysis (tofacitinib: N=586; TNFi: N=9,885; IL-17i: N=2,933). In the post-weighting tofacitinib treatment cohort, the median age was 49 years [IQR 38–57], with 69% of patient being female. In the post-weighting TNFi treatment cohort, the median age was 49 years [IQR 39–57], with 70% of patient being female. In the post-weighting IL-17i treatment cohort, the median age was 48 years [IQR 40–57], with 69% of patient being female. Across all treatment cohorts, the SMD for most features was <0.10. Before PS weighting, most demographics and baseline characteristics were imbalanced (SMDs >0.1). Excluding HCRU and costs, the biggest SMDs for the tofacitinib vs. TNFi cohort and tofacitinib vs. IL-17i cohort was noted for 'recent csDMARD use ≥30 days prior to index' (SMD 0.13 and 0.17, respectively). Similar to the AxSpA 6-month population, features where SMD >0.10 for both the tofacitinib vs. TNFi and the tofacitinib vs. IL-17i include pre-index history of advanced medications by medication, number of distinct JAKi/TNFi/non-TNFi in pre-index history, number of distinct IL-17s in pre-index history (tofacitinib vs. IL-17i cohort only), and monthly rate of AxSpA-related inpatient admissions. These features were not additionally adjusted for in the 12-month treatment failure, the 12-month HCRU and costs, or the 12-month persistence analyses. Serious infection (91–92%), mood/mental disorders (68–73%), cardiovascular disease (67–72%), and osteoarthritis (67–71%) were the most prevalent comorbid conditions pre-index. A small proportion of patients within the treatment cohorts had incomplete demographic information at index (tofacitinib: N=11 (1.9%), TNFi: N=143 (1.4%), and IL-17i: N=40 (1.4%)). The post-weighting results exclude patients with unknown sex, other only combined insurance, and/or unknown region at index. The demographic tables may be seen in the Study Results Workbook (Table 2b).

10.2.3. PsA 6-month Follow-up Population

In total, 34,817 new starts of treatment were included in the analysis (tofacitinib: N=765; TNFi: N=28,033; IL-17i: N=6,019) In the post-weighting tofacitinib treatment cohort, the median age was 55 years [IQR 46–61], with 71% of patient being female. In the post-weighting TNFi treatment cohort, the median age was 54 years [IQR 45–61], with 71% of patient being female. Before PS weighting, most demographics and baseline characteristics were imbalanced (SMDs >0.1). Excluding HCRU and costs, the biggest SMDs for the tofacitinib vs. TNFi cohort and tofacitinib vs. IL-17i cohort were noted for the history of RA (SMD 0.41), and history of csDMARD use and history of psoriasis (both SMD 0.68), respectively. In the post-weighting IL-17i treatment cohort, the median age was 54 years [IQR 46–61], with 73% of patient being female. Across all treatment cohorts, the SMD for most features was <0.10. Baseline leflunomide, history of leflunomide use, and history of RA had an SMD >0.10 in both treatment comparison cohorts (0.18 and 0.11 in tofacitinib vs. TNFi and tofacitinib vs. IL-17i, respectively). These features were not additionally adjusted for in the 6-month treatment failure analysis. Cardiovascular diseases (64–70%), osteoarthritis (64–66%), serious infection (82–84%), and psoriasis (57–61%), were the most prevalent among history of comorbid conditions. A small proportion of patients within the treatment cohorts had incomplete demographic information at index (tofacitinib: N=14 (1.8%), TNFi: N=473 (1.7%), and IL-17i: N=125 (2.1%)). The post-weighting results exclude patients with unknown sex, other only combined insurance, and/or unknown region at index. The demographic tables may be seen in the Study Results Workbook (Table 2c).

10.2.4. PsA 12-month Follow-up Population

In total, 29,154 new starts of treatment were included in the analysis (tofacitinib: N=684; TNFi: N=23,518; IL-17i: N=4,952) In the post-weighting tofacitinib treatment cohort, the median age was 55 years [IQR 46–61], with 72% of patient being female. Before PS weighting, most demographics and baseline characteristics were imbalanced (SMDs >0.1). Excluding HCRU and costs, the biggest SMDs for the tofacitinib vs. TNFi cohort and tofacitinib vs. IL-17i cohort were noted for the history of RA (SMD 0.43) and the history of psoriasis (SMD 0.69), respectively. In the post-weighting TNFi treatment cohort, the median age was 54 years [IQR 46–61], with 72% of patient being female. In the post-weighting IL-17i treatment cohort, the median age was 54 years [IQR 46–61], with 74% of patient being female. Across all treatment cohorts, the SMD for most features was <0.10. Baseline/history of csDMARD (namely leflunomide) use was the only feature where SMD >0.10 for both the tofacitinib vs. TNFi and the tofacitinib vs. IL-17i treatment comparison cohorts. This feature was not additionally adjusted for in the 12-month treatment or the 12-month persistence analyses. Serious infection (82–84%), osteoarthritis (65–66%), and cardiovascular diseases (64–71%), were the most prevalent among history of comorbid conditions. A small proportion of patients within the treatment cohorts had incomplete demographic information at index (tofacitinib: N=12 (1.8%), TNFi: N=396 (1.7%), and IL-17i: N=97 (2.0%)). The post-weighting results exclude patients with unknown sex, other only combined insurance, and/or unknown region at index. The demographic tables may be seen in the Study Results Workbook (Table 2d).

10.3. Outcome Data

All of the numbers described in Table 7. Effective Sample Sizes

concern the post-weighting effective sample sizes. The range of effective sample sizes for the tofacitinib, TNFi, and IL17i treatment cohorts were 575–815 patients, 2,610–15,428 patients, and 721–1,158 patients, respectively.

Table 7. Effective Sample Sizes

Sample	Tofacitinib	TNFi	IL-17i
6 Months follow-up			
AxSpA	815	3,511	1,158
PsA	751	15,428	1,151
12 Months follow-up			
AxSpA	575	2,610	721
PsA	672	12,992	946

10.4. Main Results

10.4.1. Primary Analysis

10.4.1.1. AxSpA 6-month Follow-up Population

After PS weighting, 28%, 32%, and 28% of patients in the tofacitinib, TNFi, and IL-17i treatment cohorts met all effectiveness criteria. No statistically significant differences in the risk of effectiveness failure were found between cohorts: TNFi vs. tofacitinib (aHR [95%CI]: 0.92 (0.84–1.01); IL-17i vs. tofacitinib (aHR [95%CI]): 1.00 (0.89–1.11). The most common events associated with effectiveness failure were low adherence to index treatment (tofacitinib 48%, TNFi 37%, IL-17i 46%), use of a new pain medication class (tofacitinib 27%, TNFi 27%, IL-17i 27%), and switching/adding another non-index advanced therapy for AxSpA (tofacitinib 20%, TNFi 15%, IL-17i 19%). The most common first events leading to effectiveness failure

were use of a new pain medication class (tofacitinib 24%, TNFi 23%, IL-17i 23%), low adherence to index treatment (tofacitinib 16%, TNFi 12%, IL-17i 15%), and switching/adding another non-index advanced therapy for AxSpA (tofacitinib 15%, TNFi 11%, IL-17i 14%). The AxSpA 6-month treatment failure results are available in the Study Results Workbook (Table 5a).

10.4.1.2. PsA 6-month Follow-up Population

After PS weighting, 38%, 37%, and 31% of patients in the tofacitinib, TNFi, and IL-17i treatment cohorts met all effectiveness criteria. No statistically significant difference in the risk of effectiveness failure was observed in the TNFi vs. tofacitinib cohorts, while a statistically significant difference in the risk of effectiveness failure was observed between the IL-17i vs. tofacitinib cohorts: TNFi vs. tofacitinib (aHR [95%CI]): 1.00 (0.91–1.10), IL-17i vs. tofacitinib (aHR [95%CI]): 1.12 (1.00–1.26). The most common events associated with effectiveness failure were low adherence to index treatment (tofacitinib 43%, TNFi 40%, IL-17i 47%), use of a new pain medication class (tofacitinib 21%, TNFi 22%, IL-17i 24%), switching/adding another non-index advanced therapy for PsA (tofacitinib 11%, TNFi 15%, IL-17i 12%). The most common first events leading to effectiveness failure were use of a new pain medication class (tofacitinib 19%, TNFi 21%, IL-17i 22%), low adherence to index treatment (tofacitinib 22%, TNFi 17%, IL-17i 22%), and switching/adding another non-index advanced therapy for PsA (tofacitinib 9%, TNFi 11%, IL-17i 10%). The PsA 6-month treatment failure results are available in the Study Results Workbook (Table 5c).

10.4.2. Secondary Analysis

10.4.2.1. AxSpA 6-month Follow-up Population

HCRU and costs were compared across the following treatment cohorts: tofacitinib vs. TNFi and tofacitinib vs. IL-17i. All reported results are from post-weighting (adjusted) analysis. The AxSpA 6-month HCRU and costs results are available in the Study Results Workbook (Table 7a). Concerning HCRU, TNFi treatment was associated with significantly higher all-cause and AxSpA-related rheumatology visits (0.18 [CI 0.14–0.23] and 0.12 [CI 0.09–0.16], respectively) and all-cause outpatient visits (0.23 [CI 0.14–0.32]), as well as significantly fewer all-cause and AxSpA-related prescription fills (-0.23 [CI -0.33– -0.14] and -0.22 [CI -0.29– -0.16], respectively) when compared to the tofacitinib cohort. In contrast, IL-17i treatment demonstrated slightly higher AxSpA-related rheumatology visits (0.04 [CI 0.01–0.06], outpatient visits (0.06 [CI 0.01–0.10]), and all-cause outpatient visit 0.17 [0.08 - 0.26] when compared to tofacitinib cohort.

Concerning costs, in 2023 US dollars, TNFi treatment was associated with significantly higher all-cause rheumatology costs ($653.12 PPPM [CI 555.26–750.98]), outpatient ($1000.50 PPPM [CI 844.96–1156.04]), total medical ($939.78 PPPM [CI 745.63–1133.93]), and total costs ($828.98 PPPM [CI 447.53–1210.43]) compared to tofacitinib. IL-17i treatment demonstrated significantly higher all-cause outpatient ($81.84 PPPM [CI -20.96–184.64]), pharmacy ($2893.28 PPPM [CI 2442.47–3344.09]), total medical ($217.60 PPPM [CI 65.65–369.54]), and total costs ($3145.72 PPPM [CI 2676.27–3615.17]), as well as higher AxSpA-related outpatient ($76.58 PPPM [CI 44.20–108.96]) and total costs ($3224.61 PPPM [CI 2794.87–3654.35]).

10.4.2.2. AxSpA 12-month Follow-up Population

Treatment failure was compared across two treatment cohorts: tofacitinib vs. TNFi and tofacitinib vs. IL-17i. After PS weighting, 14%, 14%, and 11% of patients in the tofacitinib,

TNFi, and IL-17i treatment cohorts met all effectiveness criteria. Adjusted HRs for TNFi vs. tofacitinib and IL-17i vs. tofacitinib both had confidence intervals crossing 1 and non-significant p-values, suggesting no statistically significant difference in the risk of treatment failure between treatment cohorts; TNFi vs. tofacitinib (aHR [95%CI]): 1.01 (0.92–1.12), IL-17i vs. tofacitinib (aHR [95%CI]): 1.09 (0.97–1.22). The most common events associated with effectiveness failure were low adherence to the index treatment (tofacitinib 66%, TNFi 54%, IL-17i 62%), switching/adding another non-index advanced AxSpA therapy (tofacitinib 34%, TNFi 29%, IL-17i 34%), and use of pain medication class (tofacitinib 41%, TNFi 43%, and IL-17i 44%). The most common first events leading to effectiveness failure were use of pain medication (tofacitinib 37%, TNFi 34%, IL-17i 36%), switching/adding another non-index advanced AxSpA therapy (tofacitinib 21%, TNFi 17%, IL-17i 18%), and low adherence to the index treatment (tofacitinib 9%, TNFi 8%, IL-17i 9%). The AxSpA 12-month treatment failure results may be seen in the Study Results Workbook (Table 4b).

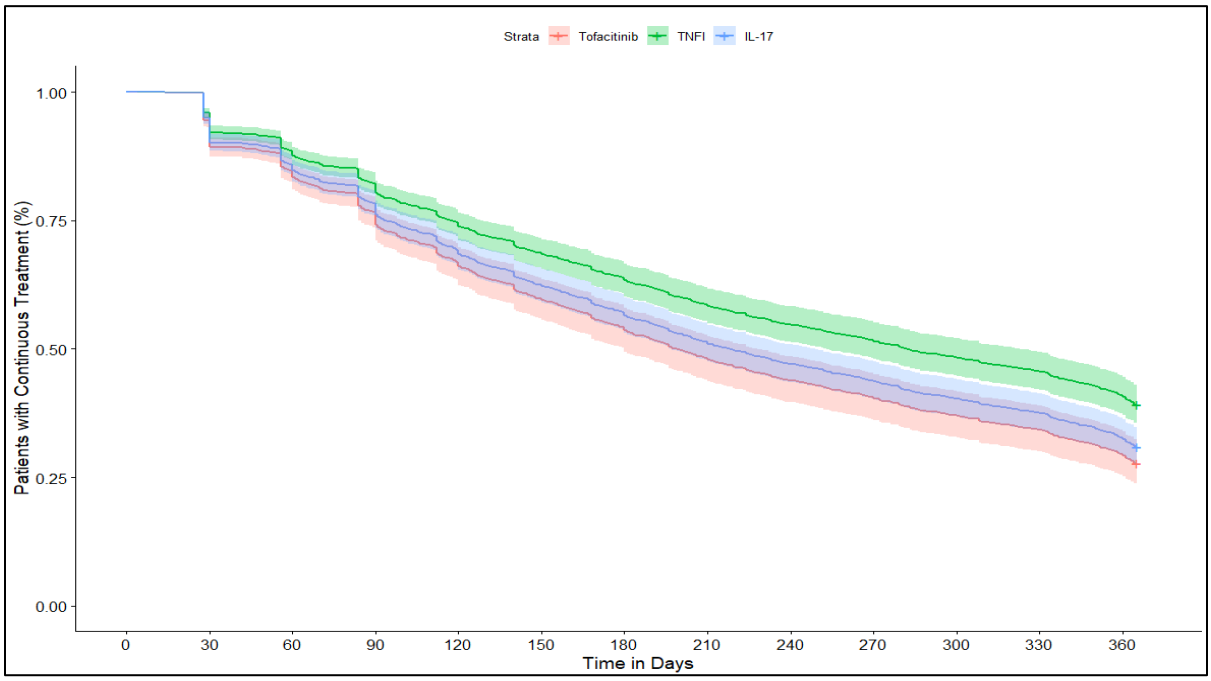
HCRU and costs were compared across two treatment cohorts; tofacitinib vs. TNFi and tofacitinib vs. IL-17i. The AxSpA 12-month HCRU and costs results may be seen in the Study Results Workbook (Table 7b). Concerning HCRU, compared to tofacitinib, TNFi treatment was associated with higher all-cause and AxSpA-associated rheumatology visits during follow-up (0.15 [CI 0.12–0.19], 0.09 [CI 0.06–0.12], respectively) and outpatient visits during follow-up (0.12 [CI 0.04–0.19], 0.10 [CI 0.06–0.14], respectively). IL-17i demonstrated higher all-cause and AxSpA-related outpatient visits during follow-up (0.14 [CI 0.06–0.21], 0.06 [CI 0.02–0.09], respectively) and prescription fills during follow-up (0.09 [CI 0.01–0.18], 0.10 [CI 0.04–0.15], respectively).

Concerning costs, in 2023 US dollars, TNFi treatment was associated with higher all-cause rheumatology visit ($526.59 PPPM [CI 439.18–614.01]), outpatient ($798.14 PPPM [CI 639.02–957.27]), total medical ($780.96 PPPM [CI 589.35–972.56]), and total costs ($564.48 PPPM [CI 151.18–977.78]) compared to tofacitinib. IL-17i demonstrated significantly higher all-cause pharmacy ($2118.97 PPPM [CI 1682.15–2555.79]) and total costs ($2141.03 PPPM [CI 1658.75–2623.32]), as well as higher AxSpA-related pharmacy ($2281.93 PPPM [CI 1856.65–2707.22]) and total costs ($2431.61 PPPM [CI 2021.84–2841.37]).

Persistence on the index medication was also compared across the following cohorts: tofacitinib vs. TNFi and tofacitinib vs. IL-17i. Over 12 months after treatment initiation, the TNFi cohort demonstrated significantly lower treatment discontinuation vs. tofacitinib cohort (lower discontinuation risk) ((aHR [95%CI]): 0.73 (0.65–0.82)), while IL-17i vs. tofacitinib treatment showed no significant difference in treatment discontinuation ((aHR [95%CI]): 0.91 (0.80–1.04)). Persistence rate was highest for TNFi and lowest for tofacitinib across all persistence time points (30, 60, 90, 180, 270, and 365 days). Median time to discontinuation

was highest for TNFi cohort (281 days) and lowest for tofacitinib cohort (199 days). The AxSpA 12-month persistence results are available in the Study Results Workbook (Table 6b).

Figure 5. AxSpA - Persistence Rate (Adjusted) KM Curves



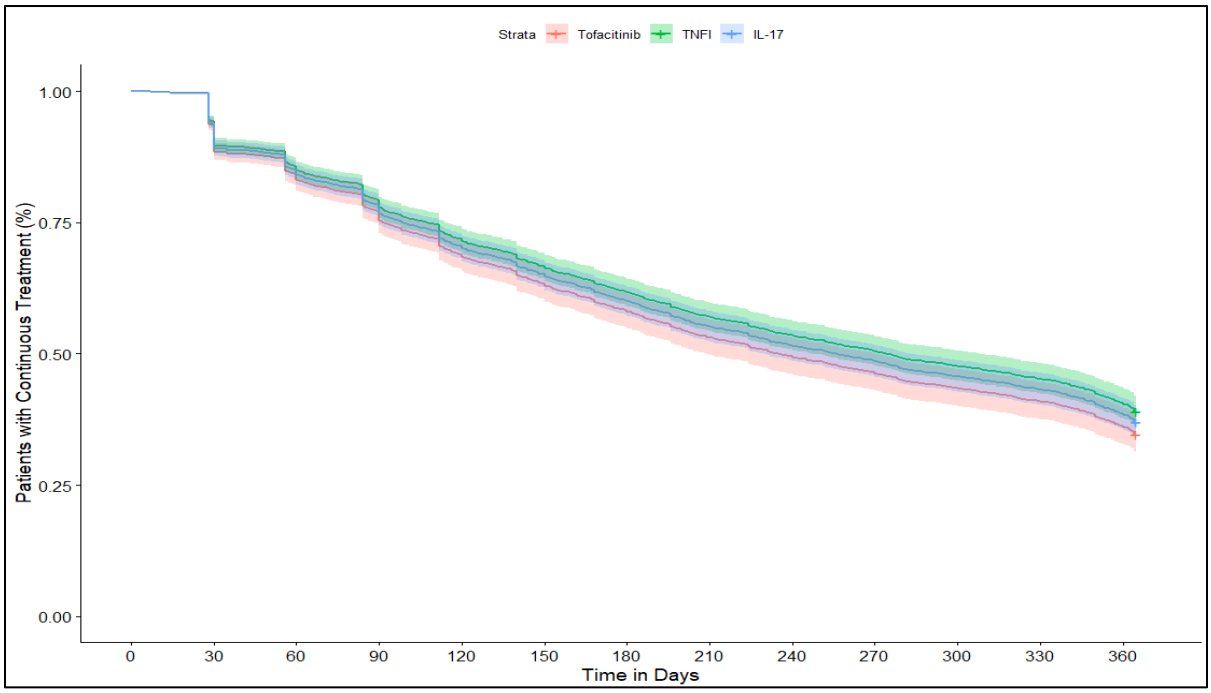
10.4.2.3. PsA 12-month Follow-up Population

Treatment failure was compared across two treatment cohorts: tofacitinib vs. TNFi and tofacitinib vs. IL-17i. After PS weighing, 17%, 19%, and 17% of patients in the tofacitinib, TNFi, and IL-17i treatment cohorts met all effectiveness criteria. Adjusted HRs for TNFi vs. tofacitinib and IL-17i vs. tofacitinib both had 95%CIs crossing 1 and non-significant p-values, suggesting no statistically significant difference in the risk of treatment failure between treatment cohorts; TNFi vs. tofacitinib (aHR [95%CI]): 0.98 (0.90–1.06), IL-17i vs. tofacitinib (aHR [95%CI]): 1.01 (0.91–1.11). The most common events associated with effectiveness failure were low adherence to index treatment (tofacitinib 60%, TNFi 57%, IL-17i 60%), use of pain medications (tofacitinib 35%, TNFi 36%, IL-17i 37%), switching/adding another non-index advanced AxSpA therapy (tofacitinib 27%, TNFi 30%, IL-17i 28%). The most common first events leading to effectiveness failure were use of pain medication (tofacitinib 31%, TNFi 31%, IL-17i 32%), switching/adding another non-index advanced AxSpA therapy (tofacitinib 16%, TNFi 18%, IL-17i 17%), and low adherence to the index treatment (tofacitinib 16%, TNFi 12%, IL-17i 14%). The PsA 12-month treatment failure results may be seen in the Study Results Workbook (Table 5d).

Persistence was compared across two treatment cohorts: tofacitinib vs. TNFi and tofacitinib vs. IL-17i. In b/tsDMARD-naïve PsA 12-month population, the TNFi cohort demonstrated significantly lower treatment discontinuation vs. tofacitinib cohort (lower discontinuation risk)

((aHR [95%CI]): 0.89 (0.81–0.98)), while IL-17i vs. tofacitinib treatment showed no significant difference in treatment discontinuation ((aHR [95%CI]): 0.93 (0.83–1.06)). Persistence rate was highest for TNFi and lowest for tofacitinib across all persistence time points (30, 60, 90, 180, 270, and 365 days). Median time to discontinuation was highest for TNFi cohort (274 days) and lowest for tofacitinib cohort (234 days). The PsA 12-month persistence results may be seen in the Study Results Workbook (Table 6d).

Figure 6. PsA - Persistence Rate (Adjusted) KM Curves



10.5. Other Analyses

Sensitivity analyses for the treatment effectiveness outcome were performed for the AxSpA 6-month and 12-month populations and the PsA 6-month and 12-month populations. Table 8. Summary of Sensitivity Analyses for AxSpA 6-month and 12-month Populations and PsA 6-month and 12-month Populations

shows the summary results of the treatment effectiveness sensitivity analyses.

Table 8. Summary of Sensitivity Analyses for AxSpA 6-month and 12-month Populations and PsA 6-month and 12-month Populations

	TNFi vs Tofacitinib aHR [95%CI]	IL-17i vs Tofacitinib aHR [95%CI]
AxSpA 6-month follow up cohort		
Primary Analysis	0.92 [0.84–1.01]	1.00 [0.89–1.11]
Sensitivity 1	0.98 [0.88–1.08]	1.01 [0.89–1.14]
Sensitivity 2	0.88 [0.81–0.97]	0.91 [0.81–1.01]
Sensitivity 3	0.92 [0.84–1.01]	1.01 [0.91–1.13]
Sensitivity 4	0.92 [0.84–1.00]	1.02 [0.92–1.14]
Sensitivity 5	0.92 [0.85–1.01]	1.00 [0.89–1.11]
AxSpA 12-month follow up cohort		
Primary Analysis	1.01 [0.92–1.12]	1.09 [0.97–1.22]
Sensitivity 1	1.02 [0.92–1.13]	1.08 [0.96–1.21]
Sensitivity 2	0.96 [0.87–1.06]	0.98 [0.88–1.10]
Sensitivity 3	1.02 [0.92–1.12]	1.09 [0.98–1.22]
Sensitivity 4	1.00 [0.91–1.11]	1.09 [0.97–1.22]
Sensitivity 5	1.02 [0.93–1.13]	1.09 [0.97–1.22]
PsA 6-month follow up cohort		
Primary Analysis	1.00 [0.91–1.10]	1.12 [1.00–1.26]
Sensitivity 1	1.11 [0.99–1.25]	1.13 [0.98–1.30]
Sensitivity 2	0.96 [0.88–1.06]	1.05 [0.94–1.18]
Sensitivity 3	1.01 [0.92–1.11]	1.13 [1.01–1.26]
Sensitivity 4	1.03 [0.93–1.13]	1.12 [1.00–1.26]
Sensitivity 5	1.00 [0.91–1.10]	1.12 [1.00–1.26]
PsA 12-month follow up cohort		
Primary Analysis	0.98 [0.90–1.06]	1.01 [0.91–1.11]
Sensitivity 1	1.04 [0.95–1.14]	1.04 [0.92–1.16]
Sensitivity 2	0.94 [0.87–1.03]	0.93 [0.84–1.04]
Sensitivity 3	0.99 [0.91–1.07]	1.02 [0.92–1.13]
Sensitivity 4	1.02 [0.93–1.11]	1.04 [0.93–1.15]
Sensitivity 5	0.98 [0.90–1.06]	1.01 [0.91–1.11]

Note. *Sensitivity 1 - Exclude criterion 1; Sensitivity 2 - Exclude criterion 3; Sensitivity 3 - Modify criterion 5 (50% increase); Sensitivity 4 - Exclude criterion 5; Sensitivity 5 - Modify criterion 3 (for patients receiving IV only, assess dose escalation based on frequency and dosage).*

Sensitivity analysis 3 and sensitivity analysis 5 in the IL-17i vs. tofacitinib PsA 6-month follow up cohort found aHRs >1 which had 95% CIs not crossing 1 and significant p-values, indicating a statistically significant higher risk of treatment failure with IL-17i compared to tofacitinib at 6 months; sensitivity analysis 3 (aHR [95%CI]): 1.13 (1.01–1.26), sensitivity analysis 5 (aHR [95%CI]): 1.12 (1.00–1.26).

10.6. Adverse Events/Adverse Reactions

In these data sources, it was not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) were not met.

11. DISCUSSION

11.1. Key Results

11.1.1. Treatment Effectiveness

AxSpA sample (Objective 1.1 & 2.1)

PS–weighted results for the AxSpA 6-month follow-up sample showed similar effectiveness across treatments cohorts with 28% (tofacitinib), 32% (TNFi), and 28% (IL-17i) of patients met all effectiveness criteria. Predominant contributors to treatment failure among patients from all three treatment cohorts included low adherence (37–48%), initiation of a new pain medication class (27%), and switching/adding another advanced therapy (15–20%). As first events leading to treatment failure, new pain medication use was most common (~23–24%), followed by low adherence (~12–16%), and switching (~11–15%). Treatment effectiveness in the AxSpA 12-month follow-up sample showed 11–14% of patients meeting the composite endpoint across treatment cohorts. Consistent with the 6-month findings, there were no statistically significant differences in the risk of effectiveness failure for TNFi or IL-17i vs. tofacitinib treatment. Predominant contributors to failure included low adherence (54–66%), therapy switching/augmentation (29–34%), and increased oral GC dose (19–23%). Most common first event leading to treatment failure included initiation of pain medication (34–37%), switching/adding another advanced therapy (17–21%), and low adherence (8–9%). Overall, results suggest treatment cohort comparable real-world effectiveness over 12 months among AxSpA patients.

PsA sample (Objective 1.2 & 2.2)

Comparative effectiveness in the b/tsDMARD-naïve PsA 6-month follow-up cohort was similar across treatment classes. After PS weighing, 38%, 37%, and 31% achieved the composite effectiveness endpoint in the tofacitinib, TNFi, and IL-17i treatment cohorts, respectively. Consistent with the AxSpA 6-month population, dominant contributors to failure were low adherence to the index therapy (40–47%), initiation of a new pain medication class (21–24%), and therapy augmentation/switching (11–15%). First events leading to treatment failure were most often new pain medication use (19–22%) or low adherence (17–22%). These results align with prior real-world patterns of comparable short-term effectiveness.

11.1.2. Persistence

AxSpA sample (Objective 2.3)

Over 12 months after treatment initiation, the TNFi cohort demonstrated significantly lower treatment discontinuation vs. tofacitinib cohort (lower discontinuation risk) ((aHR [95%CI]): 0.73 (0.65–0.82)), while IL-17i vs. tofacitinib treatment showed no significant difference in treatment discontinuation ((aHR [95%CI]): 0.91 (0.80–1.04)). These results suggest better treatment persistence with TNFi vs. tofacitinib, whereas IL-17i and tofacitinib treatment exhibited broadly similar persistence profiles. Persistence rate was highest for TNFi and lowest for tofacitinib across all persistence time points (30, 60, 90, 180, 270, and 365 days). Median time to discontinuation was highest for TNFi cohort (281 days) and lowest for tofacitinib cohort (199 days). Potential contributors to the observed differences include dosing schedules, tolerability, access, and patient preference; however, there is insufficient granularity in claims data to assess the causal reasons for persistence or lack thereof.

PsA sample (Objective 2.4)
In b/tsDMARD-naïve PsA 12-month population, the TNFi cohort demonstrated significantly lower treatment discontinuation vs. tofacitinib cohort (lower discontinuation risk) ((aHR [95%CI]): 0.89 (0.81–0.98)), while IL-17i vs. tofacitinib treatment showed no significant difference in treatment discontinuation ((aHR [95%CI]): 0.93 (0.83–1.06)). Persistence rate was highest for TNFi and lowest for tofacitinib across all persistence time points (30, 60, 90, 180, 270, and 365 days). Median time to discontinuation was highest for TNFi cohort (274 days) and lowest for tofacitinib cohort (234 days). The observed differences likely reflect treatment cohort attributes (administration route, monitoring burden, patient preference, access/cost-sharing) alongside similar 12-month effectiveness.

11.1.3. HCRU and Costs

AxSpA sample (Objective 2.5)
At both 6 months and 12 months, TNFi patients had more rheumatology and outpatient visits (all-cause and AxSpA-related) vs. tofacitinib patients; at 6 months, TNFi patients also had fewer prescription fills. Correspondingly, TNFi patients incurred higher costs when compared to patients from the tofacitinib cohort, including rheumatology, outpatient, total medical, and overall totals for both the 6-month and 12-month analyses. IL-17i patients showed modestly higher AxSpA-related rheumatology/outpatient visits and more prescription fills at 12 months and was consistently associated with higher pharmacy and total costs, including AxSpA-related totals.

11.2. Limitations
This study has several limitations which must be considered. First, the claims data lack disease severity assessments; therefore, surrogate measures (based on demographics, healthcare utilization, comorbidities, and medication history) were used as proxies for severity. Second, diagnoses of AxSpA and other conditions were identified using ICD diagnosis codes, which are subject to potential miscoding. While claims data denote the date of medication administration, fills, and days' supply information, there is no information that can confirm if the medication was consumed as prescribed, nor about reasons for treatment switching.[26,30] The Komodo database, which was used to assess treatment adherence, is a large US claims dataset that largely comprises patients with commercial health coverage; results may not be generalizable to the US population. Additionally, 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 database. In addition, while not explored in this particular study, 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. Third, the study includes only those patients who have at least 6 months or 12 months of continuous enrollment after index date to ensure there is sufficient time to assess the study outcomes in the AxSpA and PsA samples, 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. Lastly, no validation of study outcomes was conducted for this study.

11.3. Interpretation
11.3.1. Treatment Effectiveness

AxSpA sample (Objective 1.1 & 2.1)
While there are currently no other studies which directly compare treatment effectiveness among tofacitinib, TNFi, and IL-17i treated patients at 6-months and 12-months in the AxSpA sample, other comparative treatment studies are available. A study by Micheroli et al., found a comparable risk of treatment discontinuation among AxSpA patients with previous TNFi failure taking IL-17i (n=106) or an alternative TNFi (n=284); aHR [95%CI]): 1.14 (0.78–1.68) in the PS-based analysis and aHR [95%CI]): 1.16 (0.79–1.71) in the multiple-adjusted analysis. Additionally, a comparable response was found in terms of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for IL-17i vs. TNFi; (OR [95%CI]): 0.76 (0.26–2.18) and (OR [95%CI]): 0.78 (0.24–2.48) in the PS-based and the covariate-adjusted model, respectively.[31] No specific studies have been identified reporting on tofacitinib or other JAKi treatment effectiveness in AxSpA patients. However, a recent systematic review by Burhanuddin et al., found that in 11 studies (two randomized controlled trials, nine post-hoc or observational studies), tofacitinib proved effective for AS management, with efficacy maintained across various patient subgroups.[32]

Treatment effectiveness and failure among TNFi-treated patients with AxSpA is comprehensively covered in literature. In a study by Deodhar et al., TNFi treatment failure was evaluated in 1507/2866 AS patients at ≥3 months. 232 (15.4%) patients were failing current TNFi according to the definitions provided and failure rates were higher with each successive TNFi. Failure rates increased to 28.6% in patients receiving their 3rd (or later) line of TNFi (p-value < 0.001). Of the 2795 (of 2866) patients with complete treatment data, 200 (7.2%) patients switched treatment, primarily due to lack of efficacy.[33] In another study by Chmielińska et al., of 48 AxSpA patients, 21% had TNFi treatment failure (characterized by BASDAI decrease < 2 points) at 12-weeks.[34]

Finally, in a retrospective cohort study by Samartín-Ucha et al., 362 patients with chronic inflammatory arthropathies (AS (n) = 119, PsA (n) = 109) received 478 separate treatment starts of TNFi, including adalimumab, golimumab, infliximab, etanercept, or certolizumab. The most frequent causes of treatment discontinuation were therapeutic failure (44.2% and 60.8% in the AS and PsA samples, respectively) and adverse drug events (44.2% and 19.6% in the AS and PsA sample, respectively).[35] The findings from the current study report a higher proportion of treatment failure compared to recent real-world evidence research. This may be attributed to different effectiveness definitions utilized in the respective studies, or the heterogeneity in the care complexity of the study populations.

PsA sample (Objective 1.2 & 2.2)
Aligned with the 6-month results, the 12-month comparative effectiveness in b/tsDMARD-naïve PsA was similar across treatment classes, with 17–19% achieving the composite endpoint and no significant differences in failure risk for TNFi or IL-17i vs. tofacitinib. Consistent with the AxSpA results, most common drivers of failure included low adherence (57–60%), pain medication use (35–37%), and therapy switching/augmentation (27–30%). Most common first events leading to treatment failure were pain medication initiation (31–32%), switching/augmentation (16–18%), and low adherence (12–16%). These findings reinforce treatment cohort comparable 12-month effectiveness in early PsA management.

In a systematic review and network meta-analysis by McInnes et al., it was found that secukinumab, adalimumab, golimumab, and infliximab demonstrated the highest American College of Rheumatology (ACR) response rates at 16 weeks, compared to apremilast, certolizumab, etanercept, and ustekinumab. There was, however, no statistical evidence of superiority for any treatment over an active comparator.[19] In a retrospective cohort study by Zhang et al., from 2,730 PsA patients, 138 and 1,641 received IL-17i and TNFi, respectively. A claims-based algorithm validated for inflammatory arthritis treatments was used to compare treatment effectiveness. 40 (29.0%) IL-17i and 530 (32.3%) TNFi patients fulfilled effectiveness criteria at 12-months.[21] The results are comparable with those of the current study. No specific literature was identified reporting on tofacitinib or other JAKi treatment effectiveness in PsA patients.

11.3.2. Persistence

AxSpA sample (Objective 2.3)

A study by Rosenburg et al., found that the risk for discontinuation was similar for all TNFi and IL-17i regimens, regardless of biologic-experience status. The proportion of patients in the biologic-naïve cohort who had TNFi treatment discontinuation within 12 months was 34.6% for golimumab, 28.2% for etanercept, and 30.4% for adalimumab. In the biologic-experienced cohort, the 12-month discontinuation rate for IL-17i (secukinumab) treatment was 30.8% (p-value 0.3).[36] In another study by Bekele et al., 250 AxSpA patients received 731 courses of TNFi. Persistence at 12-months was reported at 84.3%.[37] The following two studies discuss 12-month persistence in both AxSpA and PsA samples. In a retrospective cohort study by Samartín-Ucha et al., 362 patients received 478 lines of biological therapy (250 (52.5%) lines in RA patients, 119 (24.9%) lines in AS patients and 109 (22.8%) lines in PsA patients), exhibiting a 71.3% (341/478) persistence at 12-months.[35] Finally, in a study by Weddell et al., 228 patients commenced IL-17i (secukinumab or ixekizumab) treatment for AxSpA or PsA were analyzed. 12-month persistence was reported at 69% [CI 63–73%] and 73% [CI 66–81%] for AxSpA and PsA patients, respectively.[38] Compared to the abovementioned results from literature, this study found lower persistence rates. However, none of the studies included a tofacitinib treatment cohort.

PsA sample (Objective 2.4)

A study by Harrold et al., found that biologic-naïve and biologic-experienced PsA patients had 12-month TNFi persistence rates at 73.8% and 63.2%, respectively. The study also found that biologic-naïve patients had a higher mean time to non-persistence compared with biologic-experienced patients: 32 vs. 23 months (p<0.001).[39] In another study, by Walsh et al., during 12-month follow-up, 73.9% of TNFi patients discontinued their index medication (26.1% persistence). Additionally, the group found that during the 12-month follow-up of adherence (i.e., PDC) among those who initiated TNFi treatment and IL-17i treatment was 0.56 and 0.65, respectively.[40] Finally, in a multicenter retrospective study by Joven et al., 221 patients treated with IL-17i (secukinumab 150mg, 103 (46.6%); secukinumab 300mg, 38 (17.2%); and ixekizumab, 80 (36.2%)) were analyzed. Persistence at 12 months on all IL-17i treatments was 81%. The group found that the most frequent reason for discontinuation across the three cohorts was lack of effectiveness (16.7%, 37/221).[41] Persistence in the current study is lower than the results described in the literature for all treatment cohorts, however, the results are comparable between treatment cohorts. Similarly to treatment effectiveness, this may be

attributed to different definitions or the heterogeneity in the care complexity of the study populations.

11.3.3. HCRU and Costs

AxSpA sample (Objective 2.5)

Considering the wider literature, there were no studies identified which directly compare costs stratified by treatment type. A 2021 study by Walsh et al. assessed both all-cause and AS-specific healthcare utilization and direct costs in US patients with AS using administrative claims data. In terms of all-cause and AS-related utilization during the 12-month follow-up period, the following key results were identified; number of inpatient admissions per patient per year (PPPY) = 1.44 and 1.08, length of inpatient stay = 5.04 and 7.75 days PPPY, patients with any ED visit = 22.5% and 2.3% PPPY, number of outpatient office visits = 10.56 and 3.36 PPPY. The group also found that during the 12-month follow-up period, patients with AS were found to have all-cause healthcare costs (mean $33,285 PPPY, median $24,978 PPPY), outpatient pharmacy costs (mean $14,074 PPPY, median $6,699 PPPY), AS-specific healthcare costs (mean $16,337 PPPY, median $10,250 PPPY), and AS-specific pharmacy costs (mean $14,595 PPPY, median $7,961 PPPY).[42] Comparing the current study to the Walsh et al. study, HCRU (all-cause inpatient admissions, all-cause ED visits) is comparable, while costs are higher in the Walsh et al. study. For instance, the current study found that for tofacitinib, TNFi, and IL-17i, the all-cause total costs were $61,212 PPPY, $67,987 PPPY, and $86,905 PPPY, compared to a mean $33,285 PPPY (median $24,978 PPPY) in the Walsh et al. study.[42] Other studies report HCRU and costs among AxSpA patients, however, not stratified by similar outcomes or by treatment, as in this study, making meaningful comparisons challenging. Additional literature is available from outside of the US, however, the healthcare and economic differences between these geographies and the US are significant. In a study by Garrido-Cumbrera et al., the HCRU behavior of 530 AxSpA patients from Spain was analyzed. 680 visits were recorded, 512 (75.3%) of which were to a rheumatologist. Half of the patients used 25 or more healthcare resources during 1 year.[43] In another study by Santos-Moreno et al., 162 Columbian patients with 2 subtypes of AxSpA were included in a costs and HCRU analysis. PPPY costs were estimated at $6,067. Medication costs accounted for 97.6% of total costs. In terms of HCRU, on average, a patient with AxSpA was seen by a rheumatologist around 4 times per year, and 95.3% of patients had ≥1 prescription of any AxSpA-related medication.[44]

11.4. Generalizability

Study results may not be generalizable outside of the insured population, or populations outside of the US Further, the Komodo dataset may not be representative of the entire US or insured population as a whole. Komodo's Healthcare Map includes longitudinal commercial, Medicaid, and Medicare Advantage claims nationwide, supporting broad payer and geographic representation, which means that uninsured and traditional Medicare fee-for-service populations may be underrepresented. The results presented in this study should not be extrapolated to pediatric patients, combination therapy (excluded), or, for b/tsDMARD-naïve PsA, prior advanced-therapy users (excluded).

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

Across AxSpA and b/tsDMARD-naïve PsA, real-world effectiveness of tofacitinib compared to TNFi and IL-17i over 6 and 12 months was comparable, though a statistically significant difference in the risk of effectiveness failure vs. IL-17i at 6 months in PsA (aHR [95% CI], 1.12 [1.00-1.26]) was observed. Persistence favored TNFi over tofacitinib in both diseases, while IL-17i showed similar persistence to tofacitinib. Health care utilization and costs in the AxSpA population were higher in the TNFi cohort compared to the tofacitinib cohort in terms of rheumatology visits (aHR [95% CI], 0.12 [0.09-0.16]), and total costs ($828.98 PPPM [CI 447.53–1210.43]), whereas the IL-17i cohort was consistently associated with higher pharmacy and total costs vs. the tofacitinib cohort ($2893.28 PPPM [CI 2442.47–3344.09] and $3145.72 PPPM [CI 2676.27–3615.17], respectively), at 6 months. These findings should be interpreted in consideration with residual confounding, claims-based proxies for effectiveness/persistence, exposure misclassification, and selection bias.

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15. LIST OF SOURCE TABLES AND FIGURES

All of the results tables and figures may be seen in the Excel Study Results Workbook:

Appendix 7. [redacted] Study Results Workbook

The following tables are contained within the embedded file.

Table/Figure	Description
Tables 0a, 0b, 0c, & 0d	Sample Excel of Unknown Demographic - 6-month/12-month follow-up period
Tables 1a & 1b	Attrition tables for Axial spondylarthritis (AxSpA) sample - 6-month/12-month follow-up period
Tables 2a	AxSpA demographic characteristics measured at index (6-month follow-up population)
Tables 2b	AxSpA demographic characteristics measured at index (12-month follow-up population)
Tables 3a	AxSpA clinical characteristics measured during the baseline period (6-month follow-up population)
Tables 3b	AxSpA clinical characteristics measured during the baseline period (12-month follow-up population)
Tables 4a & 5a	AxSpA follow-up period and treatment failure (6-month follow-up population)
Tables 4b & 5b	AxSpA follow-up period and treatment failure (12-month follow-up population)
Tables 6b & Figure 1b	AxSpA persistence on index therapy within 365 days of index treatment initiation and KM curve (12-month follow-up population)
Table 7a	All-cause and AxSpA-related healthcare resource utilization and costs within 6 months of index treatment initiation
Table 7b	All-cause and AxSpA-related healthcare resource utilization and costs within 12 months of index treatment initiation
Table 8a	Sensitivity 1 - AxSpA treatment failure - Exclude criterion 1 (6-month follow-up population)
Table 9a	Sensitivity 2 - AxSpA treatment failure - Exclude criterion 3 (6-month follow-up population)
Table 10a	Sensitivity 3 - AxSpA treatment failure - Modify criterion 5 (50% increase) (6-month follow-up population)
Table 11a	Sensitivity 4 - AxSpA treatment failure - Exclude criterion 5 (6-month follow-up population)
Table 12a	Sensitivity 5 - AxSpA treatment failure - Modify criterion 3 (6-month follow-up population)
Table 8b	Sensitivity 1 - AxSpA treatment failure - Exclude criterion 1 (12-month follow-up population)
Table 9b	Sensitivity 2 - AxSpA treatment failure - Exclude criterion 3 (12-month follow-up population)
Table 10b	Sensitivity 3 - AxSpA treatment failure - Modify criterion 5 (50% increase) (12-month follow-up population)
Table 11b	Sensitivity 4 - AxSpA treatment failure - Exclude criterion 5 (12-month follow-up population)
Table 12b	Sensitivity 5 - AxSpA treatment failure - Modify criterion 3 (12-month follow-up population)
Tables 1c & 1d	Attrition tables for Psoriatic arthritis (PsA) sample - 6-month/12-month follow-up period
Tables 2c	PsA demographic characteristics measured at index (6-month follow-up population)
Tables 2d	PsA demographic characteristics measured at index (12-month follow-up population)
Tables 3c	PsA clinical characteristics measured at during the baseline period (6-month follow-up population)
Tables 3d	PsA clinical characteristics measured at during the baseline period (12-month follow-up population)
Tables 4c & 5c	PsA follow-up period and treatment failure (6-month follow-up population)
Tables 4d & 5d	PsA follow-up period and treatment failure (12-month follow-up population)
Tables 6d & Figure 1d	PsA persistence on index therapy within 365 days of index treatment initiation and KM curve (12-month follow-up population)
Table 8c	Sensitivity 1 - PsA treatment failure - Exclude criterion 1 (6-month follow-up population)
Table 9c	Sensitivity 2 - PsA treatment failure - Exclude criterion 3 (6-month follow-up population)
Table 10c	Sensitivity 3 - PsA treatment failure - Modify criterion 5 (50% increase) (6-month follow-up population)
Table 11c	Sensitivity 4 - PsA treatment failure - Exclude criterion 5 (6-month follow-up population)
Table 12c	Sensitivity 5 - PsA treatment failure - Modify criterion 3 (6-month follow-up population)
Table 8d	Sensitivity 1 - PsA treatment failure - Exclude criterion 1 (12-month follow-up population)
Table 9d	Sensitivity 2 - PsA treatment failure - Exclude criterion 3 (12-month follow-up population)
Table 10d	Sensitivity 3 - PsA treatment failure - Modify criterion 5 (50% increase) (12-month follow-up population)
Table 11d	Sensitivity 4 - PsA treatment failure - Exclude criterion 5 (12-month follow-up population)

Table 12d	Sensitivity 5 - PsA treatment failure - Modify criterion 3 (12-month follow-up population)

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