NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Uveitis in chronic inflammatory conditions and ulcerative colitis-related pyoderma gangrenosum and axial spondylarthritis: an observational study of patients receiving advanced therapies in the United States
Protocol number	A3921444
Protocol version identifier	1.0
Date	12 January 2024
EU Post Authorization Study (PAS) register number	EUPAS107604
Active substance	L04AA29 - Tofacitinib citrate
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	*Research questions:* What is the distribution of demographic and clinical characteristics in patients with inflammatory conditions (ulcerative colitis (UC), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), and axial spondyloarthritis (axSpA)) treated with tofacitinib and other advanced treatments in the US? What is the risk of new onset anterior uveitis (AU) in patients with inflammatory conditions (UC, PsA, JIA and axSpA) treated with tofacitinib and other advanced treatments? What is the risk of new onset pyoderma gangrenosum (PG) and axial spondylarthritis (axSpA) in UC patients treated with tofacitinib and other advanced treatments? *Primary Objectives*:

	a. To describe the distributions of demographic and clinical characteristics among patients with inflammatory conditions on tofacitinib and other advanced treatments overall, and stratified by individual indication (UC, PsA, axSpA, JIA). b. To estimate crude incidence rates (IRs) of new onset AU among patients with inflammatory conditions (UC, PsA, JIA and axSpA) overall and by subset of inflammatory condition, and PG and axSpA among patients with UC, on tofacitinib and other advanced treatments. c. To estimate the adjusted hazard ratio (HR) of new onset AU in patients with inflammatory conditions (UC, PsA, JIA and axSpA) overall and by subset of inflammatory condition, PG (UC only) and axSpA (UC only) on tofacitinib compared to other advanced treatments. *Secondary Objectives*: a. To examine the stratified incidence rates and adjusted hazard ratios of AU and PG by previous history of uveitis and PG, respectively.
Author	[redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AU	Anterior uveitis
AxSpA	Axial spondyloarthritis
CDC	Centers for Disease Control
CI	Confidence interval
CPT	Current procedure terminology
EIM	Extra-intestinal manifestation
EMM	Extra-musculoskeletal manifestation
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GPP	Guidelines for Good Pharmacoepidemiology Practices
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
ICD-9	International Classification of Diseases – Ninth Revision
ICD-10	International Classification of Diseases – Tenth Revision
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IP	Inverse probability
IRB	Institutional Review Board
IR	Incidence rate

Abbreviation	Definition
ISPE	International Society for Pharmacoepidemiology
JAKi	Janus kinase inhibitor
JIA	Juvenile idiopathic arthritis
MOA	Mechanism of action
NDC	National Drug Center
NHIS	National Health Interview Survey
PASS	Post-authorization safety study
PG	Pyoderma gangrenosum
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
SAP	Statistical analysis plan
SpA	Spondyloarthritis
TNFi	Tumor necrosis factor inhibitor
UC	Ulcerative colitis
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]

4. ABSTRACT

Stand Alone document, see ANNEX 1.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	31 January 2024
End of data collection	31 December 2024
Registration in the EU PAS register	15 January 2024
Final study report	01 June 2025

7. RATIONALE AND BACKGROUND

Non-infectious uveitis is an autoimmune inflammatory condition of the uveal tissues of the eye and has a strong genetic association with *HLAB27*. Uveitis can be associated with significant visual morbidity, with over one-third of patients with uveitis having visual impairment [1]. An adequate and prompt management is required, as uveitis represent 10-20% of all preventable blindness causes in developed countries [2]. Anterior uveitis (AU), also called iridocyclitis, accounts for at least 50% of the cases of non-infectious uveitis reported, and is often associated with other autoimmune disorders, such as SpA, including axSpA, PsA and IBD-related arthritis, JIA, IBD (including Crohn's disease and UC), psoriasis, Behçet disease and sarcoidosis [3]. It has been observed that AU is the most frequent extra-musculoskeletal manifestation (EMM) of SpA (particularly in axSpA) [3] and JIA patients [4], and it is also among the most common ocular manifestations in patients with IBD (with higher prevalence in Crohn's disease compared to ulcerative colitis) [5]. In all such disorders, AU has been associated with the presence of *HLAB27* and disease duration, albeit it does not seem associated with disease activity. In some cases, uveitis can actually precede the rheumatic or autoimmune bowel disorder [3-5] and serves as a strong risk factor for diseases such as axSpA and PsA. Given the significant health burden for patients, considerations on the efficacy of the different available treatments to improve or prevent uveitis are considered among clinical management recommendations for patients with these conditions. Currently, evidence-based guidelines recommend the use of TNFi monoclonal antibodies in the presence of uveitis as EMM or extra-intestinal manifestation (EIM) [6-9].

UC poses a significant burden to patients, characterized by a heightened risk of developing EIMs which can profoundly affect patients' quality of life.[10, 11] Most EIMs emerge after an UC diagnosis is established, but often go underreported due to limited awareness by gastroenterologists or because patients do not recognize their EIM is related to their UC.[12]

EIMs can impact multiple organ systems including dermatological, ophthalmological, and musculoskeletal.[12] Categorically, the association between EIMs and UC can be viewed from three perspectives: EIMs that parallel UC activity (pauciarticular arthritis, oral aphthous ulcers, erythema nodosum, episcleritis), EIMs that have an independent course from UC activity (axial spondyloarthritis, uveitis), and EIMs that may or may not coincide with UC activity (pyoderma gangrenosum). Consequently, EIMs significantly contribute to overall morbidity and diminished quality of life experienced by UC patients.[11]

Numerous advanced therapies are available that display comparable efficacy in controlling IBD, but the efficacy regarding managing or preventing EIMs that behave independently to IBD disease activity is less known.[10] Because the use of many of these therapies has not been well studied specifically in the EIMs like axSpA, AU, and pyoderma gangrenosum (PG), current treatment guidelines for these EIMs in UC do not provide algorithms to guide clinicians in choosing an optimal regimen for their patients.[13]

Tofacitinib is a Janus kinase inhibitor (JAKi) approved for 5 indications in the US: adults with moderately to severely active rheumatoid arthritis (RA), adults with active PsA, adults with moderately to severely active UC, adults with active ankylosing spondylitis (also known as radiographic axSpA), and in patients 2 years of age or older with polyarticular course JIA.

Data on tofacitinib clinical efficacy in uveitis from the clinical trial program across all the several indications, and PG and axSpA in the UC clinical trial program, is very limited due to study design, inclusion criteria, and baseline characteristics of the different study populations, which would not allow to perform a post-hoc analysis for these outcomes. In the last years, however, several case reports and small observational studies have highlighted the potential beneficial use of JAKi (including tofacitinib) in treating uveitis as an EMM or EIM [14, 15]. In addition, there is an ongoing phase 3 trial assessing the clinical effectiveness of another JAKi , baricitinib, in JIA-associated uveitis[16].

This non-interventional study aims to provide data on the comparative clinical effectiveness of advanced therapies on incidence of uveitis among several chronic inflammatory conditions (UC, PsA, JIA, and axSpA) as well as incidence of PG and axSpA in patients with UC. The results are intended to provide useful information to healthcare professionals and patients in real-world clinical decision making on treatment choice for patients with these conditions. This non-interventional study is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Question

Research questions addressed by this study are as follows:

What is the distribution of demographic and clinical characteristics in patients with inflammatory conditions (UC, PsA, JIA, and axSpA) treated with tofacitinib and other advanced treatments in the US?

What is the risk of new onset AU in patients with inflammatory conditions (UC, PsA, JIA and axSpA) treated with tofacitinib and other advanced treatments?

What is the risk of new onset PG and axSpA in UC patients treated with tofacitinib and other advanced treatments?

8.1.1. Primary Objectives

The primary objectives for this study are:

a. To describe the distributions of demographic and clinical characteristics among patients with inflammatory conditions on tofacitinib and other advanced treatments overall, and stratified by individual indication (UC, PsA, axSpA, JIA).

b. To estimate crude incidence rates (IRs) of new onset AU among patients with inflammatory conditions (UC, PsA, JIA and axSpA) overall and by subset of inflammatory condition, and PG and axSpA among patients with UC, on tofacitinib and other advanced treatments.

c. To estimate the adjusted hazard ratio (HR) of new onset AU in patients with inflammatory conditions (UC, PsA, JIA and axSpA) overall and by subset of inflammatory condition, PG (UC only) and axSpA (UC only) on tofacitinib compared to other advanced treatments.

8.1.2. Secondary Objectives

a. To examine the stratified incidence rates and adjusted hazard ratios of AU and PG by previous history of uveitis and PG, respectively.

9. RESEARCH METHODS

9.1. Study Design

This is a population-based retrospective cohort study of adults (ages ≥18 years of age) with axSpA, PsA, and UC, and children ≥2 years with JIA identified through a US data source.

9.2. Setting

The populations under study will be patients diagnosed with UC, PsA, axSpA, or JIA with an index date between 31 May 2018 and 30 November 2023 (for UC), between 15 December 2017 and 30 November 2023 (for PsA), or between 18 November 2021 and 30 November 2023 (for axSpA), and children ≥2 years of age diagnosed with JIA with an index date between 28 September 2020 and 30 November 2023. This study will use the US Komodo's Healthcare Map administrative claims database, which captures data sufficiently representative of the US population with the diseases of interest. Identification of disease populations, outcomes of interest, and drugs prescribed will be implemented using International Classification of Diseases – Ninth Revision (ICD-9) or International Classification of Diseases – Tenth Revision (ICD-10) codes, current procedure terminology (CPT) procedure codes, and prescribing data (eg, National Drug Center (NDC) codes) in the patients' records.

9.2.1. Definition of Study Cohort

Upon establishing that a patient has an indication of interest, patients will be followed from subsequent date of new drug initiation (index date) until the earliest date of death, end of study period, the event of interest, treatment switch, treatment discontinuation (+ 90 days), or end of enrollment in the database.

Exposure to therapies will be defined using the NDC for dispensed medications and, where relevant, procedure codes for injection or infusion. New users will be defined as those with a prescription for a drug they had not previously been prescribed during the baseline period (365 days prior to index date).

Treatment discontinuation will be defined as a period of >90 days without a dispensation of the same treatment (or up to 9 months for rituximab) after the period covered by the previous reimbursement, or switch date to another biologic or advanced treatment (ie, date of reimbursement). Further information is defined in the statistical analysis plan (SAP).

9.2.1.1. Exposure

Exposure within and across the disease populations will be classified according to mechanism of action (MOA):

Exposure Category	MOA	Medication	UC	PsA	axSpA	JIA
1	JAKi	tofacitinib	X	X	X	X
2	JAKi	tofacitinib or upadacitinib	X	X	X	
3	IL-12/-23i	ustekinumab	X	X		X
4	α4β7 integrin inhibitor	vedolizumab	X			
5	TNFi (monoclonal)	adalimumab, golimumab, infliximab; or certolizumab pegol (for PsA, axSpA, and JIA)	X	X	X	X
7	IL-23i	risankizumab or guselkumab		X		
8	IL-17i	secukinumab; or ixekizumab (PsA and axSpA)		X	X	X
9	CTLA-4i	abatacept		X		X
10	PDE4 inhibitor	apremilast		X		
11	TNFi-(receptor)	etanercept		X	X	X
12	IL-6i	tocilizumab				X
13	anti-CD20	rituximab				X

9.2.2. Inclusion Criteria

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

1. Aged ≥18 years at index date for PsA, UC, and axSpA; aged ≥2 years at index date for JIA.

2. Evidence of at least 2 inpatient or outpatient diagnosis codes ≥30 days apart for axSpA, JIA or PsA on or prior to index date (index date is the date of drug initiation), with at least one diagnosis code by a rheumatologist; or evidence of at least 1 inpatient or 2 outpatient diagnosis codes ≥30 days apart for UC on or prior to index date.

3. Evidence of initiation for at least 1 approved advanced treatment for the corresponding identified indication as defined in Section 9.2.1.

4. At least 365 days of continuous enrollment in database prior to index date.

5. At least 90 days of continuous enrollment in database after index date.

9.2.3. Exclusion Criteria

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

1. Combination therapy, with more than 1 advanced therapy prescribed simultaneously on index date.

2. Other advanced treatment users with a history of use of any JAK inhibitor.

3. Individuals who are pregnant at or within 9 months of index date.

9.2.3.1. Additional Exclusion Criteria for PsA, JIA and axSpA

For the PsA, JIA and axSpA patient cohorts, patients meeting any of the following additional exclusion criteria will not be included in the study:

1. Evidence of at least 1 inpatient or 2 outpatient diagnosis codes ≥30 days apart for RA.

9.2.3.2. Additional Exclusion Criteria for JIA

For the JIA patient cohort, patients meeting any of the following additional exclusion criteria will not be included in the study:

1. Evidence of at least 1 inpatient or 2 outpatient diagnosis codes ≥30 days apart for systemic JIA (ICD-10 code M08.2).

9.2.3.3. Additional Exclusion Criteria for UC

For the UC patient cohort, patients meeting any of the following additional exclusion criteria will not be included in the study:

1. Evidence of at least 1 inpatient or 2 outpatient diagnosis codes ≥30 days apart for Crohn's disease.

9.3. Variables

Variables utilized in this study include baseline demographics and clinical characteristics, comorbidities, and medications. All variable definitions will be specifically defined in the SAP, including code lists and time periods of interest. Outcomes of interest analyzed in the study are listed in Table 1.

Table 1. Variables Defining Safety Outcomes

Variable	Role	Operational definition[a]
SAFETY OUTCOMES		
Non-infectious anterior uveitis (AU)	Outcome	Diagnosis (inpatient or outpatient) of non-infectious AU after index date, further specified in the SAP
Pyoderma gangrenosum (PG; UC only)	Outcome	Diagnosis (inpatient or outpatient) of PG after index date, further specified in the SAP
Axial spondylarthritis (axSpA; UC only)	Outcome	Diagnosis (inpatient or outpatient) of axSpA after index date, further specified in the SAP

a. Where applicable codes and other definitions to be further defined in the SAP.

9.4. Data Sources

This study will utilize a US data source, Komodo's Healthcare Map. This is a real-world dataset which integrates disparate sources of patient-level data to map longitudinal patient journeys. Komodo pulls de-identified, patient-level claims data from Clearinghouse, Payer (150+ payer), and Provider data sources to follow patients as they move through the healthcare system. The patient-centric database is enriched with data from electronic medical records and other sources. Komodo's closed dataset (payer complete dataset) allows researchers to conduct a robust claims-based analysis with a large sample size and long follow-up periods. Regardless of the data source, continuous enrollment is the key criterion for research-grade data extraction. Komodo's closed dataset (payer complete dataset) will be used for this analysis.

Komodo currently has real world data on more than 325 million patients that are well-distributed geographically across the US. Table 2 illustrates this further by comparing Komodo's 2019 patient population (from closed dataset) with the CDC's 2019 National Health Interview Survey (NHIS) of insured patients. The database covers all the US census regions. The all-payer claims data is fullyadjudicated. Komodo's Healthcare Map is a patient-centered claims dataset that complies with HIPAA.

Table 2. Regional Distribution of Komodo Health Dataset (Updated 06 June 2022)

U.S. Region	Komodo Data	NHIS 2019
Northeast	19.5%	16.9%
South	38.0%	36.5%
Midwest	21.6%	22.2%
West	20.9%	24.4%

Table 3. Age Distribution of Komodo Health Dataset

Age Range	Komodo	NHIS 2019
0 – 9	11.7%	11.3%
10 – 19	12.0%	12.3%
20 – 29	10.9%	9.6%
30 – 39	11.6%	12.6%
40 – 49	11.5%	11.3%
50 – 59	13.7%	12.8%
60 – 69	13.8%	14.4%
70 – 79	9.4%	9.9%
80+	5.5%	5.6%

Table 4. Gender Distribution of Komodo Health Dataset

Gender	Komodo Data oi	NHIS 2019
Female	54.8%	54.0%
Male	45.2%	46.0%

9.5. Study Size

Preliminary feasibility (as per July 2023) analyses indicate sample sizes of 5,319, 1,228, 1,435 and 3,851 new tofacitinib users with at least 12 months of continuous enrollment for PsA, axSpA, JIA and UC populations, respectively, in the Komodo dataset.

9.6. Data Management

All study data exist as structured data by the time of study. Analyses will be conducted using statistical software such as SAS, R, SQL and/or Python. Versions of packages will be documented to assure reproducibility.

9.7. Data Analysis

An overview of the planned analyses is provided below.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Descriptive Analyses

Baseline demographic and clinical characteristics will be tabulated across all disease cohorts (UC, PsA, axSpA, and JIA) as well as among each disease cohort, and each exposure category across and within the disease cohorts, using frequencies and proportions for categorical variables, and means, standard deviations, medians, and interquartile ranges for continuous variables. Comorbidities and history of prescription medications will be measured and described with summary statistics for the baseline look-back period of 12 months prior to the index date, unless otherwise specified.

9.7.2. Incidence Rates

Number of events, person-years at risk, and crude incidences will be calculated for each outcome. IRs for select safety events will be calculated with person-time at risk starting on the index date and ending on the date of a censoring event: 1) death, 2) end of study period, 3) the event of interest, 4) treatment switch, 5) treatment discontinuation (+ 90 days), or 6) end of enrollment in the database.

IRs per 100 person-years will be calculated based on the number of new events divided by the sum of the duration of patient exposures from the index date to censoring date during the risk period.

Details for handling observable person time will be detailed in the SAP.

IRs of outcomes will be calculated for each exposure outlined in Section 9.2.1.1 among the individual and combined populations according to MOA where overlapping exposure categories are present. If cases per disease population are deemed insufficient, analysis stratified by Rheumatology and Gastroenterology indications will be performed. Given differences in age distribution, JIA patients may be analyzed separately from other patient populations.

9.7.3. Comparative Analyses: Hazard Ratios using Inverse Probability Weighting to Control for Confounding

Hazard rates ratios will be estimated using an inverse probability (IP) weighted Cox proportional hazards model with time since treatment start as timescale for each outcome. All assumptions of the Cox proportional hazards model will be tested to ensure appropriate use. IP weighting will be used to control for potential confounding variables at baseline and selected based on *a priori* knowledge and statistical properties of the cohorts under study for each outcome. Statistical methods for IP weighting will be detailed in the SAP. The model will also incorporate censoring. Variables incorporated into the weighting may be reassessed if not successfully implemented (eg, model fails to converge).

9.7.4. Subgroup Analyses

IRs and HRs will be stratified by the following factors:

1. History of uveitis or PG for each corresponding outcome analysis (history determined by prior ICD codes for uveitis or PG and related conditions) (yes/no).

Additional subgroup analyses will be conducted as sensitivity analyses (further described in the SAP), such as stratification by TNFi monoclonal use 12 months prior to index date (yes/no), and

previous biologic or other advanced treatment use prior to baseline (yes/no), should sample size allow.

9.7.4.1. Sensitivity Analyses

Sensitivity analyses will be conducted and are detailed in the SAP.

9.8. Quality Control

Analyses are programmed according to the specifications in the protocol, and if applicable, the SAP, and documented in a programming plan. Final deliverables will be reviewed and verified by a second, independent programmer who may also perform double programming. All quality checks will be documented in the programming plan.

9.9. Strengths and Limitations of the Research Methods

The Komodo database is large and covers a wide geographic area; however, limitations that are general to all claims database analyses as well as those specific to this study should be noted. Disease diagnoses will be identified using ICD-9-CM and/or ICD-10-CM diagnosis codes, which are subject to potential miscoding, though presumably without respect to the treatment or outcomes. Where possible, validated algorithms will be used. The baseline period of this study is of limited duration thus baseline comorbidities and risk factors occurring outside of this baseline period may not be captured, which may lead to misclassification.

Information on prescriptions for outpatients does not necessarily indicate that the medication was consumed or taken as prescribed; similarly, medications filled over-the-counter or provided as samples by the physician will not be recorded in the database.

Cases not requiring treatment or office visits tend to be systematically under-recorded in such databases; therefore, it is possible that this study will only capture severe manifestations of such disorders.

Outcomes were also captured by way of medical claims, which may have some degree of misclassification. To reduce the potential for misclassification of outcomes, outcomes were defined using definitions previously validated in healthcare data, such as claims databases where possible. Additionally, follow-up time may not be sufficient to capture all outcomes.

Study results may not be generalizable outside of the insured population, or populations outside of the US.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

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

10.2. Patient Consent

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

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

As this study involves only the use of de-identified data, no IRB/IEC approval is necessary.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

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

13. REFERENCES

1. Rothova, A., et al., *Causes and frequency of blindness in patients with intraocular inflammatory disease.* Br J Ophthalmol, 1996. **80**(4): p. 332-6.
2. Gritz, D.C. and I.G. Wong, *Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study.* Ophthalmology, 2004. **111**(3): p. 491-500; discussion 500.

3. Cantini, F., et al., *Uveitis in Spondyloarthritis: An Overview.* J Rheumatol Suppl, 2015. **93**: p. 27-9.
4. Clarke, S.L., E.S. Sen, and A.V. Ramanan, *Juvenile idiopathic arthritis-associated uveitis.* Pediatr Rheumatol Online J, 2016. **14**(1): p. 27.
5. Troncoso, L.L., et al., *Ophthalmic manifestations in patients with inflammatory bowel disease: A review.* World J Gastroenterol, 2017. **23**(32): p. 5836-5848.
6. Ramiro, S., et al., *ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update.* Ann Rheum Dis, 2023. **82**(1): p. 19-34.
7. Coates, L.C., et al., *Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021.* Nat Rev Rheumatol, 2022. **18**(8): p. 465-479.
8. Angeles-Han, S.T., et al., *2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis.* Arthritis Care Res (Hoboken), 2019. **71**(6): p. 703-716.
9. Pytrus, W., et al., *A Review of Ophthalmic Complications in Inflammatory Bowel Diseases.* J Clin Med, 2022. **11**(24).
10. Ferretti, F., et al., *The impact of biologic therapies on extra-intestinal manifestations in inflammatory bowel disease: A multicenter study.* Front Med (Lausanne), 2022. **9**: p. 933357.
11. Sange, A.H., et al., *Extra-Intestinal Manifestations of Inflammatory Bowel Disease.* Cureus, 2021. **13**(8): p. e17187.
12. Jansen, F.M., et al., *Clinical management of the most common extra-intestinal manifestations in patients with inflammatory bowel disease focused on the joints, skin and eyes.* United European Gastroenterol J, 2020. **8**(9): p. 1031-1044.
13. Greuter, T., et al., *Emerging treatment options for extraintestinal manifestations in IBD.* Gut, 2021. **70**(4): p. 796-802.
14. Chen, J.L., P. Abiri, and E. Tsui, *Recent advances in the treatment of juvenile idiopathic arthritis-associated uveitis.* Ther Adv Ophthalmol, 2021. **13**: p. 2515841420984572.
15. Gupta, N. and D. Mahajan, *ACR Convergence 2022 Abstract Supplement.* Arthritis Rheumatol, 2022. **74 Suppl 9**.
16. Ramanan, A.V., et al., *Clinical effectiveness and safety of baricitinib for the treatment of juvenile idiopathic arthritis-associated uveitis or chronic anterior antinuclear antibody-positive uveitis: study protocol for an open-label, adalimumab active-controlled phase 3 clinical trial (JUVE-BRIGHT).* Trials, 2021. **22**(1): p. 689.

14. LIST OF TABLES

Variables utilized in this study include baseline demographics and clinical characteristics, comorbidities, and medications. All variable definitions will be specifically defined in the SAP, including code lists and time periods of interest. Outcomes of interest analyzed in the study are listed in Table 1.

Table 3. Age Distribution of Komodo Health Dataset

Age Range	Komodo	NHIS 2019
0 – 9	11.7%	11.3%
10 – 19	12.0%	12.3%
20 – 29	10.9%	9.6%
30 – 39	11.6%	12.6%
40 – 49	11.5%	11.3%
50 – 59	13.7%	12.8%
60 – 69	13.8%	14.4%
70 – 79	9.4%	9.9%
80+	5.5%	5.6%

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 4	02 Jan 2024	Abstract

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.