# The Risk of Non-Infectious Uveitis Among Patients Treated with Remicade® Compared to Other Biologic Treatments

**Protocol PCSIMMA0051**

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|---|---|
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| **Prepared By:** | Janssen Research & Development, LLC |
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# 1. LIST OF ABBREVIATIONS

AS - ankylosing spondylitis
ATC - Anatomical Therapeutic Chemical code
CCAE - IBM® MarketScan® Commercial Database
CCDS - Core Company Data Sheet
CD - Crohn's Disease
CDM - Common Data Model
CI - confidence intervals
CPT - Current Procedural Terminology
d - day
DOD - Date of Death
Dx - diagnosis
EASE - Expected Absolute Systematic Error
EMA - European Medicine's Agency
EMR - electronic medical record
FDA - Food and Drug Administration
HR - hazard ratio
IC - information component
ICD - International Classification of Diseases
IRB - Institutional Review Boards
ITT - Intent to Treatment
LASSO - least absolute shrinkage and selection operator
OMOP - Observational Medical Outcomes Partnership
OT - On-Treatment
PASS - Post-Authorization Safety Study
PBRER - Periodic Benefit-risk Evaluation Reports
PRAC - Pharmacovigilance Risk Assessment Committee
PS - propensity score
PsA - psoriatic arthritis
PsO - psoriasis
PSUR - Periodic Safety Update Report
PV - pharmacovigilance
RA - rheumatoid arthritis
RR - relative risk
Rx - prescription/exposure
SARS - Severe Acute Respiratory Syndrome
SMD - standardized mean difference
SMT - Safety Management Team
TAR - Time-at-Risk
TGA - Therapeutic Goods Administration
TNF - tumor necrosis factor
TNFai - TNF alpha inhibitor
UC - ulcerative colitis
US - United States

# 2. RESPONSIBLE PARTIES

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# 3. ABSTRACT

Several biologic agents indicated for the treatment of Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis have been reported to be associated with an increased risk of uveitis. One regulatory agency updated their Remicade® and infliximab biosimilars product labels to include a uveitis risk based on case report disproportionality analyses. This observational, population-level effect estimation study will quantify the risk of non-infectious uveitis among new users of Remicade® relative to comparator biologics in patients with Crohn's disease or ulcerative colitis, psoriasis or psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis using real-world data from routine clinical care in the United States. A priori, the study design, conditional on the data analyzed, has been empirically evaluated to assess its ability to generate valid comparative risk estimates and will inform which results will be reported.

# 4. AMENDMENTS AND UPDATES

Currently none.

**Table 1 - Amendments and Updates**

| Number | Date | Section of study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| | | | | |
| | | | | |

# 5. RATIONALE AND BACKGROUND

Remicade® (infliximab) was the first tumor necrosis factor (TNF) alpha inhibitor biologic approved in 1998 for the treatment of rheumatoid arthritis (RA) in combination with methotrexate. Since the initial approval, several other indications followed, including Crohn's Disease (CD) (adult and pediatric), ulcerative colitis (UC) (adult and pediatric), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and chronic severe plaque psoriasis. There are three United States (US) Food and Drug Administration (FDA) approved biosimilars to Remicade®: Inflectra®, Reneflexis®, and Avsola™.

In 2014, the European Medicine's Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) requested Janssen to monitor anterior uveitis for the 3-year Periodic Safety Update Reports (PSURs)/Periodic Benefit-risk Evaluation Reports (PBRER). Janssen's review of available data at the time concluded that there was insufficient evidence to conclude that uveitis or anterior uveitis was causally associated with infliximab. In addition, the assessment found that there was no pattern in presenting symptoms or latencies and that many cases were confounded by underlying disease, co-suspect drugs or concomitant medications, and prior medical conditions. No changes were made to the infliximab Core Company Data Sheet (CCDS). In 2017, PRAC agreed with Janssen's conclusions, and no further actions were required. Since 2017, the routine pharmacovigilance (PV) assessments did not identify uveitis as a safety signal.

In 2021, the Australian Therapeutic Goods Administration (TGA) recommended inclusion of uveitis as a "side effect" to Remicade in the Australian PI based on disproportionate reporting of events from October to December 2020. They detected 8 case reports of uveitis associated with infliximab, with a Proportional Reporting Ratio (PRR) value of 7.45 and a positive information component (IC) value of 2.39; the GMS guidance indicates that the MHRA considers a PRR ≥3 as the threshold for signal detection[1]. A further search of the VigiBase database using search terms Infliximab and Uveitis in February 2021 noted 276 global cases (IC=2.5 and $IC_{025}$=2.3). Janssen reviewed available evidence and disagreed with the TGA's assessment and concluded that there was insufficient evidence to warrant the label change to include uveitis as a risk. TGA disagreed with our conclusion and required the label update for uveitis, which harmonized the Australian labels for Remicade® with infliximab biosimilars for uveitis.

In preparation for possible inquiries on this topic from other health authorities, the Remicade® Safety Management Team (SMT) requested that Global Epidemiology evaluate the feasibility of an observational study to further examine the potential association of non-infectious uveitis with Remicade®. This study would aim to provide additional evidence for regulatory decision-making and for potential use in future communications with TGA and/or other health authorities. After extensive assessment, Global Epidemiology concludes that an observational study is feasible and proposes a study to estimate and compare the risk of non-infectious uveitis among patients treated with Remicade® versus other candidate comparators. All analyses will be done separately for each indication for Remicade®. This study was not requested by any health authority and is therefore a voluntary Post-Authorization Safety Study (PASS), with the results to be reported in the Remicade® PBRER.

# 6. STUDY OBJECTIVES

## 6.1. Primary Objectives

To examine if exposure to Remicade®, by indication, causes an increased risk of non-infectious uveitis, during a specified time-at-risk period, relative to comparator biologics within the same indication.

# 7. RESEARCH METHODS

## 7.1. Study Design

This study will follow a retrospective, observational, active comparator, new-user cohort design [2]. We define 'retrospective' to mean the study will be conducted using data already collected prior to the start of the study. We define 'observational' to mean there is no intervention or treatment assignment imposed by the study investigators and that the data are collected during routine clinical care. We define 'cohort' to mean a set of patients satisfying one or more inclusion criteria for a duration of time. We define 'comparative cohort design' to mean the formal comparison between two cohorts, a target cohort and comparator cohort, for the risk of an outcome during a defined time-period after cohort entry.

## 7.2. Data Sources

Data sources used are described in Table 2 and include 3 US-based health plan or insurance claims databases, one US-based electronic medical record (EMR) data source, and one US-based electronic health record (EHR) data source.

All data sources have been standardized to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) [3], version 5.3. The OMOP CDM includes a standard representation of health care experiences (such as information related to drug utilization and condition occurrences), common vocabularies for coding clinical concepts, and enables consistent application of analysis across multiple disparate data [3]. The completed specification for the OMOP CDM is available at: https://github.com/OHDSI/CommonDataModel. Details about the model can be found at: https://ohdsi.github.io/CommonDataModel/. Documentation on the database transformations to the CDM can be found at: https://github.com/OHDSI/ETL-CDMBuilder/tree/master/man.

All analyses will be performed independently within each of these five data sources to produce a set of five results.

**Table 2 – Description of Data Sources**

| IBM® MarketScan® Commercial Claims and Encounters Database (CCAE) | |
|---|---|
| **Version ID** | V2044 |
| **Database Start Date** | 2000-01-01 |
| **Database End Date** | 2022-01-31 |
| **Database Description** | The IBM® MarketScan® Commercial Database (CCAE) includes health insurance claims across the continuum of care (i.e., inpatient, outpatient, outpatient pharmacy, carve-out behavioral healthcare) as well as enrollment data from large employers and health plans across the United States who provide private healthcare coverage for more than 155 million employees, their spouses, and dependents. This administrative claims database includes a variety of fee-for-service, preferred provider organizations, and capitated health plans. |
| **IQVIA Adjudicated Health Plan Claims Data (IQVIA_PHARMETRICS_PLUS)** | |
| **Version ID** | V2001 |
| **Database Start Date** | 2013-01-01 |
| **Database End Date** | 2021-11-30 |
| **Database Description** | The IQVIA Adjudicated Health Plan Claims Data (formerly PharMetrics Plus) – a United States of America (US) database comprised of fully adjudicated health plan claims data and enrollment information for commercial individuals. The information is comprised of over 70 contributing health plans and self-insured employer groups throughout the US for over more than 140 million unique enrollees since 2006. This anonymous, patient-centric database includes all medical and pharmacy claims data (costs and descriptive services). Claims represent payments to providers for services rendered to covered health plan individuals. The data also includes patient-level enrollment which is a record of demographic variables including eligibility status (year of birth, gender, US Census region, eligibility by month). The enrollee population in the database is generally representative of the less than 65 years of age, commercially insured population with a subset of Commercial Medicare and Medicaid in the US with respect to both age and gender. The average length of enrollment is 39 months, and 47 million patients have 3 or more years of continuous enrollment (medical and pharmacy coverage). Each contributing plan's data undergoes rigorous data quality review by IQVIA prior to its addition to the IQVIA Adjudicated Health Plan Claims - US database. |
| **Optum© De-Identified Clinformatics® Data Mart Database – Date of Death (DOD) (OPTUM_DOD)** | |
| **Version ID** | 2050 |
| **Database Start Date** | 2000-05-01 |
| **Database End Date** | 2021-12-31 |
| **Database Description** | Optum's Clinformatics® Data Mart is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans. The database includes approximately 17-19 million annual covered lives, for a total of over 65 million unique lives over a 12-year period (1/2007 through 12/2019). Clinformatics® Data Mart is statistically de-identified under the Expert Determination method consistent with HIPAA and managed according to Optum® customer data use agreements. Administrative claims submitted for payment by providers and |

**Table 2 – Description of Data Sources**

| | |
|---|---|
| | pharmacies are verified, adjudicated and de-identified prior to inclusion. This data, including patient-level enrollment information, is derived from claims submitted for all medical and pharmacy health care services with information related to healthcare costs and resource utilization. The population is geographically diverse, spanning all 50 states. Optum Clinformatics® Data Mart Date of Death (Optum DOD) also provides date of death (month and year only) for members with both medical and pharmacy coverage from the Social Security Death Master File (however after 2011 reporting frequency changed due to changes in reporting requirements) and location information for patients is at the US state level.<br><br>Optum requests review of work prior to submitting for publication. |
| **IQVIA Ambulatory Electronic Medical Records (IQVIA_AMB_EMR)** | |
| **Version ID** | V1979 |
| **Database Start Date** | 1995-01-01 |
| **Database End Date** | 2021-12-24 |
| **Database Description** | The IQVIA Ambulatory EMR asset is comprised of approximately 90+ million patient records with a face-to-face physician interaction since 2006 and are sourced from an "opt-in" provider research network.<br><br>The aggregated database comprises records collected by over 100,000 physicians from large practices and physician networks located in all 50 US states. Approximately 40% of the contributing physicians are primary care practitioners and the remaining are specialists.<br><br>Key information collected includes:<br>• Patient age/ gender / race / 3-digit ZIP/longitudinal tracking<br>• Vitals (e.g., blood pressure, heart rate, weight, height)<br>• Risk factors (e.g., smoking, alcohol), co morbidities, medical history<br>• Lab tests performed and results<br>• Allergies and vaccine details<br>• Diagnoses (ICD-9, ICD-10)<br>• Prescription drugs prescribed, administered (strength, form, quantity, frequency, days' supply, refills, DAW, start and stop dates)<br>• Procedures performed/other treatments (CPT)<br>• SNOMED-CT codes<br>• Recording of patient care episodes (encounters, visits, appointments, correspondence, etc.)<br><br>Incremental data contributions are processed monthly. Users will typically see a 45-day lag before new information is added to the database.<br><br>The information collected allows linking key clinical variables such as lab values and blood pressure to therapeutic outcomes and to prescriptions / diagnosis / hospital metrics and connecting patient vitals, health behaviors and risk factors to diagnosis and treatment. |

**Table 2 – Description of Data Sources**

| **Optum EHR** | |
|---|---|
| **Version ID** | V2247 |
| **Database Start Date** | 2007-01-01 |
| **Database End Date** | 2022-03-01 |
| **Database Description** | Optum's longitudinal EHR repository is derived from dozens of healthcare provider organizations in the United States, that include more 57 contributing sources and 111K sites of care and includes approximately 107 million patients. The data is certified as de-identified by an independent statistical expert following HIPAA statistical de-identification rules and managed according to Optum® customer data use agreements. Clinical, claims and other medical administrative data is obtained from both Inpatient and Ambulatory electronic health records (EHRs), practice management systems and numerous other internal systems. Information is processed, normalized, and standardized across the continuum of care from both acute inpatient stays and outpatient visits. Optum® data elements include demographics, medications prescribed and administered, immunizations, allergies, lab results (including microbiology), vital signs and other observable measurements, clinical and inpatient stay administrative data and coded diagnoses and procedures. In addition, Optum® uses natural language processing (NLP) computing technology to transform critical facts from physician notes into usable datasets. The NLP data provides detailed information regarding signs and symptoms, family history, disease related scores (i.e., RAPID3 for RA, or CHADS2 for stroke risk), genetic testing, medication changes, and physician rationale behind prescribing decisions that might never be recorded in the EHR. |

## 7.3. Study Populations

We are studying four indication populations: 1.) Crohn's disease or ulcerative colitis (CD/UC), 2.) ankylosing spondylitis (AS), 3.) moderate to severe plaque psoriasis or psoriatic arthritis (PsO/PsA), and 4.) rheumatoid arthritis (RA). Nested within each indication population we will compare a target versus a comparator cohort. The target cohorts represent our exposure of interest, Remicade®, where the index is defined by the first exposure to that drug. The comparator cohorts represent the drugs to which we will compare Remicade®, where the index is also defined by the first exposure to any of the drugs considered. For each comparison, the Target cohort and Comparator cohort will be limited to the period after the earliest approval date of any drug in the Comparator cohort for that respective indication. Table 3 shows which drug comparisons are made within each indication population and the earliest approval date for the Comparator cohort.

| Table 3 – Drug Comparisons made by Indication | | | | | |
|---|---|---|---|---|---|
| **Indication** | **Target Cohorts** | **Target Approval Date** | **Comparator Cohorts** | **Comparator with First Approval Date** | **Comparator with Most Recent Approval Date** |
| Crohn's Disease [CD] or Ulcerative Colitis [UC] | Remicade® | 8/24/1998 | golimumab, certolizumab pegol, ustekinumab, or vedolizumab | 4/22/2008 (certolizumab pegol) | 9/26/2016 (ustekinumab) |
| Ankylosing Spondylitis [AS] | Remicade® | 12/17/2004 | golimumab, certolizumab pegol, ixekizumab, or secukinumab | 4/24/2009 (golimumab) | 8/26/2019 (ixekizumab) |
| Plaque psoriasis [PsO] or Psoriatic arthritis [PsA] | Remicade® | 5/13/2005 | golimumab, certolizumab pegol, guselkumab, risankizumab, tildrakizumab, brodalumab, ixekizumab, secukinumab, or ustekinumab | 4/24/2009 (golimumab) | 4/23/2019 (risankizumab) |
| Rheumatoid Arthritis [RA] | Remicade® & Methotrexate* | 11/10/1999 | certolizumab pegol or tocilizumab | 5/13/2009 (certolizumab pegol) | 1/11/2010 (tocilizumab) |

* Remicade® should be administered in combination with methotrexate for the treatment of RA

The following sections, Indication Cohorts, Target Cohorts, and Comparator Cohorts, provide more details on how patients were found. An intersection between the indication and exposure cohorts were made to find indication-exposure specific cohorts. We wanted people who both had the indication and a given exposure, as long as the indication occurred prior to or on the day of the first exposure of the drug. Figure 1 shows at a high level how the indication cohorts are combined with the exposure cohorts.

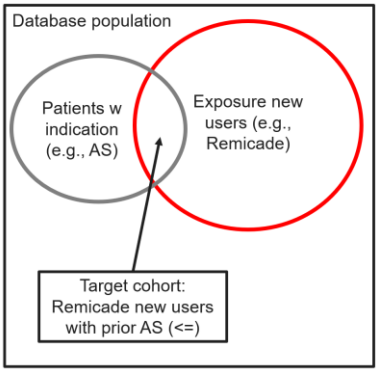


**Figure 1 – Depiction of the intersection of indication and exposure cohorts**
*AS = Ankylosing Spondylitis*

The comparison drugs were selected because they were identified as approved biologics for treatment of a specific indication. Additionally, specific drugs were not considered for comparison if there was published evidence that they either increased or decreased the risk for uveitis. For example, etanercept and adalimumab were excluded from all comparisons. Etanercept is known to increase the risk of uveitis

and adalimumab is approved as a treatment for uveitis, as well as known to decrease the risk of uveitis [4, 5].

ATLAS, with a combination of SQL, will be used to generate the target and comparator cohorts that are needed to perform this study. "ATLAS is an open-source software tool for researchers to conduct scientific analyses on standardized observational data converted to the OMOP [CDM]" [6]. All concept sets used within this study can be found in Appendix 16.1. Additionally, we will use CohortDiagnostics to review all cohorts. CohortDiagnostics is a tool for interrogating cohorts instantiated on a database [7]. The URL for CohortDiagnostics for this project can be found here:

https://sharedshiny-prod.jnj.com/user/jweave17/epi_964_6_cohort_diagnostics/

### 7.3.1. Indication Cohorts

These cohorts will be used to find indications prior to the exposure in the target and comparator cohorts. A high-level description of these cohorts is finding the first diagnosis of the condition. The cohorts were developed using a phenotype process that applies definitions across a set of databases and empirically examines alternative definitions using CohortDiagnostics. See Appendix 16.2 for specific details on each indication cohort.

- **Crohn's Disease or Ulcerative Colitis (CD/UC)**
  https://epi.jnj.com/atlas/#/cohortdefinition/9028

- **Ankylosing Spondylitis (AS)**
  https://epi.jnj.com/atlas/#/cohortdefinition/9048

- **Moderate to severe plaque psoriasis or Psoriatic arthritis (PsO/PsA)**
  https://epi.jnj.com/atlas/#/cohortdefinition/9029

- **Rheumatoid Arthritis (RA)**
  https://epi.jnj.com/atlas/#/cohortdefinition/8449

### 7.3.2. Target Cohorts

The 4 target cohorts are new users of Remicade®. New use is defined as the first exposure on the patient record provided 365 days of prior observation time. The target cohorts are also biologic-naïve through restricting to patients without prior exposure to the drugs listed in the cohort definitions below. If a subject was exposed to an infliximab biosimilar before Remicade® they are excluded. The target cohorts are restricted to adults (>=18 years of age at index). The study end date is 12/31/2021 because 2022 data are incomplete in our data sources.

Inferred persistent exposure will allow no more than a 90-day gap[1] between successive exposures (persistence window) plus 90 days added surveillance to the last exposure date (surveillance window).

[1] Based on an empirical assessment the durations between injections for the drugs in the data sources included in this study, where 90 days was found to include most of the patients; from a safety assessment standpoint, this was the most conservative approach and was chosen as the follow-up duration. See Appendix 16.10 for distributions of time between subsequent exposures for the study drugs.

This approach is consistent with safety follow-up in registry regulatory safety studies for Janssen biologics) [8]. Because of variable drug exposure end date -and days' supply capture across data sources for infusion or injectable products, drug exposures will be forced to a 1-day supply to ensure consistent 90 persistent windows are applied. Inferred persistent exposure is censored if a comparator exposure, other TNF alpha inhibitor (TNFai), or interleukin inhibitor is observed. If a patient discontinues treatment without a subsequent switch, the exposure window will end at the end of the surveillance window (i.e., date of last exposure + 90-day surveillance window). See Appendix 16.3 for additional information on persistence and surveillance windows.

Finally, Remicade® new users are grouped by indication for indication-nested analyses. This means, for a given indication, patients must have a diagnosis before or concurrent with their first Remicade® exposure. Additionally, the first Remicade® exposure must occur on or after the US FDA approval date for that indication (See Table 3).

URLs to the fully specified target cohort definitions with indication-specific inclusion/exclusion are listed below:

- **Remicade with CD/UC**
  https://epi.jnj.com/atlas/#/cohortdefinition/9369
  - Patients have no prior exposure to other TNFai (adalimumab, certolizumab pegol, etanercept, golimumab) or interleukin inhibitors. And additionally, no prior vedolizumab or natalizumab.
  - Exposure window ends on adalimumab, etanercept, golimumab, certolizumab pegol, vedolizumab, natalizumab, and Interleukin inhibitors.

- **Remicade with AS**
  https://epi.jnj.com/atlas/#/cohortdefinition/9373
  - Patients have no prior exposure to other TNFai (adalimumab, certolizumab pegol, etanercept, golimumab) or interleukin inhibitors.
  - Exposure window ends on adalimumab, etanercept, golimumab, certolizumab pegol, and Interleukin inhibitors.

- **Remicade with PsO/PsA**
  https://epi.jnj.com/atlas/#/cohortdefinition/9371
  - Patients have no prior exposure to other TNFai (adalimumab, certolizumab pegol, etanercept, golimumab) or interleukin inhibitors.
  - Exposure window ends on adalimumab, etanercept, golimumab, certolizumab pegol, and Interleukin inhibitors.

- **Remicade and methotrexate with RA**
  https://epi.jnj.com/atlas/#/cohortdefinition/9367
  - Patients have no prior exposure to other TNFai (adalimumab, certolizumab pegol, etanercept, golimumab) or interleukin inhibitors. And additionally, no prior abatacept.
  - Must also experience an exposure to methotrexate between 30 days prior to index through 30 days post index.

- Exposure window ends on adalimumab, etanercept, golimumab, certolizumab pegol, abatacept, and Interleukin inhibitors.

Figure 2 depicts the temporal cohort definition logic for the "Remicade® with AS" cohort. Other target cohorts follow similar patterns.

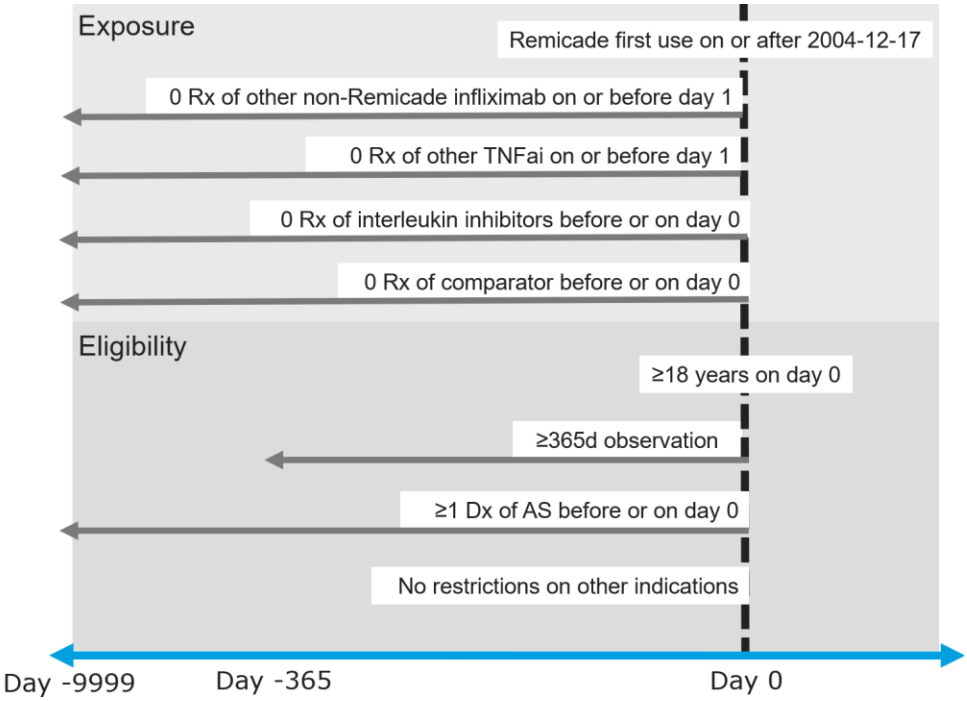


**Figure 2 – Diagram of the Remicade with Ankylosing Spondylitis (AS) Cohort**
*Dx = diagnosis, Rx = prescription/exposure, d = day, AS = Ankylosing Spondylitis*

See Appendix 16.4 for detailed descriptions of these cohorts.

### *7.3.3. Comparator Cohorts*

Comparator cohorts were selected based on the indication being compared to Remicade® (Table 3). In general, these cohorts are new users of one of the ingredients being compared to; the exposure is the first in the record and the patients have 365 days of observable time prior to index. The patients are greater than or equal (>=) 18 years of age at index. The study end date is 12/31/2021 because 2022, currently, has incomplete data in our data sources.

Inferred persistent exposure will allow no more than a 90-day gap[2] between successive exposure intervals (persistence window) plus 90 days added surveillance to the last exposure date (surveillance

[2] Based on an empirical assessment the durations between injections for the drugs in the data sources included in this study, where 90 days was found to include most of the patients; from a safety assessment standpoint, this was the most conservative approach and was chosen as the follow-up duration. See Appendix 16.10 for distributions of time between subsequent exposures for the study drugs.

window) (an approach consistent with safety follow up in registry regulatory safety studies for Janssen biologics) [8]. Drug exposures will be forced to be a 1-day supply. This persistent exposure window is censored if an exposure to a drug in the comparator cohort, other TNFai, or interleukin inhibitors is recorded. See Appendix 16.3 for additional information on surveillance and persistence windows.

Finally, comparator new users are grouped by indication for indication-nested analyses. This means, for a given indication, patients must have a diagnosis of the indication before or concurrent with their first comparator drug exposure. Additionally, that exposure must occur on or after the approval date for that indication (See Table 3).

Figure 3 above, while for "Remicade® with AS", depicts the temporal cohort definition logic for the comparator cohorts. URLs to the fully specified comparator cohort definitions with indication-specific inclusion/exclusion are listed below:

- **golimumab, certolizumab pegol, ustekinumab, vedolizumab with CD/UC**
  https://epi.jnj.com/atlas/#/cohortdefinition/9370
  - Patients have no prior exposure to other TNFai (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) or interleukin inhibitors. And additionally, no prior natalizumab.
  - Exposure window ends on infliximab, adalimumab, etanercept, natalizumab, interleukin inhibitors (excluding ustekinumab).

- **certolizumab pegol, golimumab, ixekizumab, secukinumab with AS**
  https://epi.jnj.com/atlas/#/cohortdefinition/9374
  - Patients have no prior exposure to other TNFai (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) or interleukin inhibitors.
  - Exposure window ends on infliximab, adalimumab, etanercept, interleukin inhibitors (excluding ixekizumab and secukinumab).

- **golimumab, certolizumab pegol, guselkumab, risankizumab, tildrakizumab, brodalumab, ixekizumab, secukinumab, or ustekinumab with PsO/PsA**
  https://epi.jnj.com/atlas/#/cohortdefinition/9372
  - Patients have no prior exposure to other TNFai (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) or interleukin inhibitors.
  - Exposure window ends on infliximab, adalimumab, etanercept, interleukin inhibitors (excluding brodalumab, guselkumab, ixekizumab, Risankizumab, secukinumab, tildrakizumab, ustekinumab).

- **certolizumab pegol, tocilizumab with RA**
  https://epi.jnj.com/atlas/#/cohortdefinition/9368
  - Patients have no prior exposure to other TNFai (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) or interleukin inhibitors. And additionally, no prior abatacept.

- Exposure window ends on infliximab, adalimumab, etanercept, golimumab, abatacept, and Interleukin inhibitors (excluding tocilizumab).

See Appendix 16.5 for detailed descriptions of these cohorts.

### *7.3.4. Population Subgroups*

There are no additional patient subgroups.

## 7.4. Outcomes of Interest

### *7.4.1. Outcome Cohorts*

**Non-infectious uveitis**
https://epi.jnj.com/atlas/#/cohortdefinition/8466

The outcome definition for non-infectious uveitis is:

1. a diagnosis of non-infectious uveitis or iridocyclitis followed by at least one more diagnosies between 31 and 365 days after the first occurrence
   OR
2. a diagnosis of non-infectious uveitis or iridocyclitis during a visit associated with an ophthalmology provider specialty.

To be eligible for the analysis, patients will be required to not have a history of a uveitis event in their history (i.e., all available patient history in data source). Thus, all events included in this analysis will be the first known uveitis event in the available patient record.

Figure 3 depicts the outcome cohort definition. For full specification see Appendix 16.6.

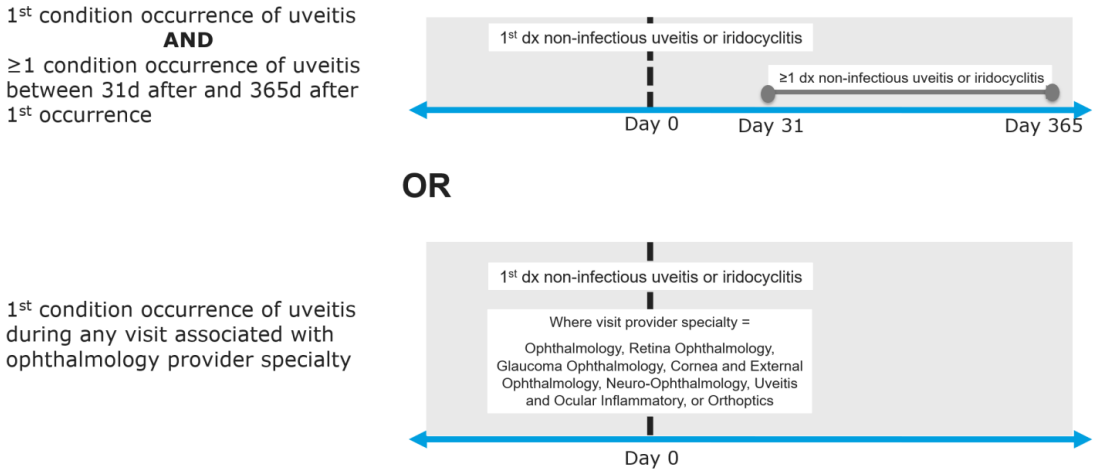


**Figure 3 – Cohort Definition for non-infectious uveitis**
*d = day, dx = diagnosis*

Examination of the outcome cohort characteristics were completed by the study team and an ophthalmologist to ensure that the non-infectious uveitis phenotype was valid and clinically appropriate.

### *7.4.2. Negative Control Outcome Cohorts*

Negative control outcomes are conditions known to not be causally associated with the target or comparator exposure cohorts, such that we can assume the true relative risk between the exposures is 1. For further details, including the process used to select negative controls, see Voss et al.[9] The 88 negative control outcomes for the present study are listed in Appendix 16.7, where a diagnosis record for each condition is used to define a single negative control cohort. We include all descendant conditions when defining each negative control outcome cohort.

The same analysis that will be performed for each pairwise comparison to assess the risk of non-infectious uveitis will also be performed to assess the risk of each negative control outcome. Because the negative control qualifying criteria support the a priori assertion of no effect, we assume the true relative risk (RR) for each negative control outcome is 1, and the difference between RR=1 and the observed effect estimate will be considered error, encompassing both random and systematic effects. We will be able to calibrate the non-infectious uveitis hazard ratio and confidence intervals against the empirical null distribution which is fit from the estimates for the negative control outcomes [10, 11].

## 7.5. Exposures of Interest

Discussed in the sections labeled “Target Cohorts” and “Comparator Cohorts”.

## 7.6. Tools

This study will be designed using OHDSI tools [12] (specifically ATLAS and the Population-Level Estimation tools) and run with R [13].

# 8. SAMPLE SIZE AND STUDY POWER

The sample size of the cohorts prior to matching are reported in Table 4.

**Table 4 – Number of Subjects in Target, Comparator, and Outcomes before study design restrictions**

| Cohort | Optum | CCAE | Optum EHR | Pharmetrics | Amb EMR |
|---|---|---|---|---|---|
| Remicade and methotrexate w RA | 3,629 | 4,219 | 4,173 | 1,418 | 2,195 |
| certolizumab pegol, tocilizumab w RA | 4,164 | 2,898 | 7,617 | 7,152 | 4,751 |
| Remicade w CD-UC | 11,835 | 19,307 | 19,737 | 22,451 | 8,191 |
| golimumab, certolizumab pegol, ustekinumab, vedolizumab w CD-UC | 5,969 | 7,079 | 13,959 | 17,765 | 6,981 |
| Remicade w PsO-PsA | 1,967 | 2,802 | 3,007 | 3,721 | 1,493 |
| golim, certz, guselk, risankiz, tildrakiz, brodal, ixekiz, secukin, ustekin PsO-PsA | 11,481 | 18,899 | 19,878 | 31,061 | 11,120 |
| Remicade w AS | 875 | 1,290 | 1,044 | 1,658 | 491 |

| | | | | | |
|---|---|---|---|---|---|
| certolizumab pegol, golimumab, ixekizumab, secukinumab w AS | 925 | 1,115 | 1,436 | 2,258 | 713 |
| Non-infectious uveitis (primary) | 260,779 | 292,132 | 71,977 | 176,396 | 25,626 |

Small sample sizes of some exposure cohorts and subgroup exposure cohorts may limit the ability to generate population-level effect estimates for which valid inferences can be made. For example, small exposure cohort sample sizes may limit the ability of the PS adjustment strategy to achieve acceptable covariate balance in a pairwise comparison or in conjunction with outcome event occurrence may be underpowered to detect an estimate of a meaningful magnitude. Rather than deciding a priori to not make certain comparisons based on power, this study will generate a full set of population-level effect estimation diagnostics, including empirical calibration, for all pre-specified pairwise comparisons, which will be blinded until study diagnostics is complete; the estimates for target-comparator-outcome-analysis-databases combinations that acceptably pass all study diagnostics will be unblinded and reported. Consistent application of pre-specified methods in high throughput observational studies may reduce results reproducibility problems observed when study design decisions are made on a study- or comparison-specific basis [14].

# 9. DATA ANALYSIS PLAN

## 9.1. Time-at-Risk

### *9.1.1. Primary - On-Treatment*

On-treatment time-at-risk (TAR) will be defined as the time ranging from the cohort start date (i.e., index) to the end of inferred persistent exposure, end of continuous observation, or exposure to any other target or comparator drug, whichever comes first. This is known as an on-treatment (OT) TAR.

As previously described, a persistence window of 90-days will be applied to create periods of inferred persistent exposure, with a 90-days surveillance window added to the last exposure date. Based on the distribution in days between drug exposures, the 90-days persistence window will create periods of inferred persistent exposure for 90% of sequential exposure records for most drugs in most databases. While drugs with shorter dosing frequencies may be misclassified as having continuous exposure, the distributions in Appendix 16.10 suggests that most patients are receiving treatment at the labeled dose frequency. Therefore, we do not believe that the use of the 90-days persistence window will result in disproportionate misclassification of continuous exposure in drugs with shorter dosing frequencies (e.g., certolizumab pegol) compared to drugs with longer dosing frequencies (e.g., ustekinumab).

### *9.1.2. Sensitivity - Intent to Treat*

The intent-to-treat (ITT) TAR starts on the index date and continues until the target or comparator cohort ends observable time within the data source.

## 9.2. Candidates Baseline Patient Characteristics

Baseline characteristics will be compared between exposure groups using standardized differences and those differences will be considered meaningful if they exceeded a threshold of 10%, as has been previously used in the literature [15, 16].

Baseline characteristics will include the following, but which covariates are selected for balancing will depend on a selection process (see Section 9.3.1) implemented within each condition and database:

- Demographics (age in 5-year bands, sex, race, ethnicity, index year, index month)
- All conditions occurrence records aggregated to SNOMED clinical finding level during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
- All drug exposure records aggregated to RxNorm ingredient level and Anatomical Therapeutic Chemical code (ATC) classes during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
    - persistent exposure that overlaps index date
- All procedure occurrence records during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
- Measurements (including laboratories) within, above, and below normal range during the following lookback window:
    - in 365 days prior to and including index date
- Device exposure records during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
- Comorbidity or risk scores described below are calculated using all available time prior to index date:
    - Charlson Comorbidity Index
    - DCSI
    - CHADS2
    - CHADS2VASc

## 9.3. Model Specification

### *9.3.1. Propensity Score Model Specification*

Propensity scores (PS) will be used as an analytic strategy to reduce potential confounding due to imbalance of subject characteristics at baseline between the target and comparator cohorts. The PS is the probability of a subject being classified in the target cohort versus the comparator cohort, given a set of observed covariates (listed out in section Patient Characteristics Summary). The PS will be estimated for each subject using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross validation, using a starting variance of 0.01 and a tolerance of 2e-7.

Covariates that occur in fewer than 0.1% of the combined target and comparator cohort will be excluded before model fitting for computational efficiency. Covariates correlated with exposure status (Pearson correlation coefficient >0.5) are assessed manually and not included in the PS model if considered an exposure proxy. Appendix 16.8 contains covariates excluded from the PS models (typically because they are associated with the target or comparator drug in some way).

### 9.3.2. Propensity Score Matching Strategy

We will employ two matching strategies. Those strategies are:

- Primary: 1:10 variable ratio propensity score matching
- Sensitivity: 1:1 propensity score matching

This approach will use a greedy matching algorithm by applying a caliper of 0.2 of the standard deviation on the logit scale of the PS distribution.

### 9.3.3. Outcome Model Specification

Within each indication and database, a Cox proportional hazards regression model with treatment as the only explanatory variable will be used to model the time to the first outcome occurrence for the target group relative to the comparator group while accounting for the PS matching. Estimates of risk will be generated as the empirically calibrated hazard ratios (HR), 95% confidence intervals (CI), and p-values. The uncalibrated HR, CI, and p-value will also be reported. The number of persons, days amount of time-at-risk, and number of outcome events in each cohort in each pairwise comparison after PS matching will also be reported.

For each target-comparator-outcome-analysis combination, heterogeneity of the hazards ratios across databases will be estimated, using $I^2$ as a metric, and reported [17]. If there is sufficient homogeneity across databases ($I^2$<40%) [18], database-specific estimates will be pooled through random effect meta-analysis (using a DerSimonian–Laird estimate of the random-effect variance). In this case, the pooled point estimate and confidence interval will be reported, as well as the p-value, corresponding to a hypothesis test for a point null hypothesis of the hazard ratio equal to one (against the alternative that the hazard ratio is not equal to one). Where heterogeneity across sources is greater than $I^2$≥40%, a pooled estimate will not be generated and point estimates and confidence intervals from individual databases will be reported with hypothesis testing. When pooled estimates are reported, hypothesis tests may be overly sensitive to detecting effects given the databases have some patient overlap (i.e., dependent data). Similarly, the DerSimonian–Laird random-effects meta-analysis may also be overly sensitive to detecting effects because it can underestimate the random-effect variance resulting in narrower confidence intervals.

## 9.4. Evidence Evaluation

### 9.4.1. Propensity Score Distribution

Once the PS model is fit for each pairwise comparison, the PS distribution for the target and comparator cohort will be plotted to evaluate the comparability, as a proxy for exchangeability, of the two cohorts before matching. The plot will be scaled to the preference score, which normalizes for initial cohort size

imbalance. If the proportion of patients in clinical equipoise, i.e. the patients with a preference score between 0.3 and 0.7, is less than 35%, then the estimate will not be reported [19].

### 9.4.2. Covariate balance before and after propensity score matching

Covariate balance will be evaluated by plotting the standardized mean difference (SMD) of each covariate before against the SMD after propensity score matching. After matching SMDs with values of <0.1 are asserted to indicate negligible group differences [19]. All covariates need to have a value <1.0 to pass diagnostics.

### 9.4.3. Outcomes Greater Than 0

We did not require a specific minimal detectable relative risk; however, we required that outcome occurrences during the time-at-risk period for both the target and comparator were greater than 0.

### 9.4.4. Expected Absolute Systematic Error

We used the negative control outcome effect estimates to fit an empirical null distribution quantifies residual error inherent to the study design conditional on the data analyzed. The expected absolute systematic error (EASE) summarizes the systematic error component of the empirical null distribution[20] and represents the difference between the observed and expected negative control outcome effect estimates as a single measure. Higher EASE values represent greater residual bias and lower EASE values represent less residual bias. We considered analyses with EASE>0.25 to have failed the diagnostic.

## 9.5. Analyses to Perform

The comprehensive set of analyses will result in 80 effect estimates. There will be one effect estimate for each data source by indication-nested comparison, by PS matching strategy, by TAR.

$$5\ data\ sources\ \times 4\ indication\ comparisons \times 2\ PS\ matching \times 2\ TAR\ \times 1\ outcome = \ 80\ analysis\ results$$

The total number of analyses will further increase based on the number of meta-analyses that are ultimately conducted, given acceptable homogeneity across databases.

## 9.6. Output

Covariate balance before and after matching will be summarized in tabular form by showing the mean value for all baseline covariates in the target and comparator cohort, with the associated standardized mean difference computed for each covariate.

Once the propensity score model is fit, we will plot the propensity score distribution of the target and comparator cohorts before PS adjustment to evaluate initial comparability of the two cohorts. The plot will be scaled to the preference score, normalizing for any imbalance in cohort size. The covariates selected within the propensity score model, with associated coefficients will also be reported.

Covariate balance will be evaluated by plotting the standardized mean difference of each covariate before PS adjustment against the standardized mean difference for each covariate after PS stratification.

An attrition diagram will be provided to detail the loss of patients from the original target cohort and comparator cohort to the subpopulations that remain after all design considerations have been applied. The outcome model, a conditional Cox proportional hazards model, will be summarized by providing the uncalibrated and calibrated hazards ratios (see section Negative Control Cohorts) and the associated 95% confidence interval. The number of persons, time-at-risk, and outcome counts in each cohort will also be reported.

Effect estimate generalizability will be assessed by calculating and plotting standardized mean differences of all covariates between the original target cohort and the final target cohort that remains after design considerations (e.g., PS matching) have been applied. Similarity implies that the effect estimates are applicable to the original target population. Dissimilarity implies that the effect estimates are applicable to the final target cohort only, and generalizability must be interpreted cautiously.

# 10. STUDY DIAGNOSTIC RESULTS

All comparative effect estimation evidence evaluation results are available in an interactive, web-based application available on the JNJ network:
https://sharedshiny-prod.jnj.com/user/jweave17/epi_964_7_estimation_diagnostics/

Table 5 reports the 19 database-analysis-comparison combinations that meet (pass) MDRR, covariate balance, equipoise, and EASE validity diagnostics. See Section 9.4 – Evidence Evaluation for rules used. Population-level effect estimates for combinations that meet the 4 validity diagnostics will be reported. Appendix 16.9 reports the full diagnostic results for all 80 database-analysis-comparison combinations.

| Table 5 - Database-analysis-comparison combinations that pass validity diagnostics | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Database** | **Analysis variant** | **Indication** | **Target exposure** | **Comparator exposure** | **T events** | **C events** | **MDRR** | **Max SMD** | **Equipoise** | **EASE** |
| Amb EMR | 1:1 PS matched, on-treatment | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 3 | 1 | 16.47 | 0.089 | 0.422 | 0.241 |
| | 1:1 PS matched, ITT | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 2 | 4 | 9.85 | 0.086 | 0.422 | 0.004 |
| | 1:10 PS matched, ITT | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 2 | 4 | 10.19 | 0.082 | 0.422 | 0.008 |
| Pharmetrics Plus | 1:1 PS matched, on-treatment | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 12 | 30 | 2.37 | 0.047 | 0.431 | 0.105 |
| | 1:1 PS matched, ITT | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 27 | 50 | 1.89 | 0.047 | 0.431 | 0.126 |
| | 1:10 PS matched, on-treatment | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 12 | 42 | 2.20 | 0.047 | 0.431 | 0.074 |
| | 1:10 PS matched, ITT | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 27 | 68 | 1.81 | 0.047 | 0.431 | 0.099 |
| Optum EHR | 1:1 PS matched, on-treatment | RA | Remicade and methotrexate | certolizumab pegol, tocilizumab | 5 | 1 | 9.85 | 0.096 | 0.558 | 0.049 |
| | 1:1 PS matched, on-treatment | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 4 | 5 | 6.47 | 0.055 | 0.480 | 0.156 |
| | 1:1 PS matched, ITT | RA | Remicade and methotrexate | certolizumab pegol, tocilizumab | 10 | 8 | 3.75 | 0.093 | 0.557 | 0.083 |
| | 1:1 PS matched, ITT | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 18 | 23 | 2.40 | 0.058 | 0.481 | 0.147 |
| | 1:10 PS matched, on-treatment | RA | Remicade and methotrexate | certolizumab pegol, tocilizumab | 5 | 4 | 7.78 | 0.097 | 0.558 | 0.141 |
| | 1:10 PS matched, on-treatment | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 4 | 7 | 5.65 | 0.055 | 0.480 | 0.087 |
| | 1:10 PS matched, ITT | RA | Remicade and methotrexate | certolizumab pegol, tocilizumab | 10 | 21 | 3.02 | 0.086 | 0.557 | 0.063 |
| | 1:10 PS matched, ITT | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 18 | 26 | 2.38 | 0.058 | 0.481 | 0.147 |
| CCAE | 1:1 PS matched, on-treatment | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 10 | 11 | 3.40 | 0.072 | 0.387 | 0.122 |
| | 1:1 PS matched, ITT | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 23 | 30 | 2.16 | 0.07 | 0.386 | 0.165 |
| | 1:10 PS matched, on-treatment | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 10 | 18 | 2.95 | 0.071 | 0.387 | 0.107 |
| | 1:10 PS matched, ITT | CD-UC | Remicade | golimumab, certolizumab pegol, ustekinumab, vedolizumab | 23 | 41 | 2.05 | 0.068 | 0.386 | 0.153 |

# 11. STRENGTHS AND LIMITATIONS

## 11.1. Strengths

- Use of five large US-based real-world data sources, which capture information on biologic treatment utilization and safety outcomes of interest that reflect a broad variety of real-world settings where biologics are prescribed.
- Comparative cohort study with PS adjustment to enable comparisons, where appropriate, based on extensive diagnostics.
- Comprehensive clinical characterization of patients with non-infectious uveitis to ensure validity of the outcome cohort definition. An ophthalmologist reviewed the characterization.
- Use of negative control outcomes to assess systematic error in the study design.

## 11.2. Limitations

- Patients may switch health insurance; limited follow up time due to insurance changes may impact the ability to assess safety outcomes of interest.
- Capture of treatments (including target, comparator, or concomitant medications) obtained outside of health insurance or in other systems of care (e.g., over the counter medications) cannot be assessed.
- For EMR/EHR data sources, it is possible that ophthalmologic care patients receive outside of the network is not captured and included in this analysis.
- There are limitations associated with the ascertainment and identification of uveitis in real-world settings that stem from the lack of standardization of nomenclature and coding. While ICD codes are helpful in identifying patients with uveitis, inherent weaknesses of this approach should be considered (e.g., non-specificity of coding practices, misclassification of etiology, misdiagnosis).
- For study diagnostics, the preference score was lowered to 35% (from 50%) to enable generation of output (as opposed to failing diagnostics at the higher threshold) but this also impacts the generalizability of the estimation results as the analytic population and target populations may be different.
- As the study is based on claims databases, other clinical measures of interest (e.g., lab test values, patient reported outcomes, anthropometric measures, etc.) cannot be assessed.
- The study results will not necessarily be generalizable to all patients in the United States. Generalizability may be further compromised based on patient loss due to use of PS matching techniques.
- The COVID-19 is a pandemic where infected people may develop Severe Acute Respiratory Syndrome (SARS) and it is possible that during the pandemic that the exposures and outcomes could have gone uncaptured in these databases. However, we reviewed the impacts of the COVID-19 timeline on our cohorts and did not see a material difference between the incidence rates of those cohorts between before and after the pandemic started.
- The study includes only adult patients with a prior diagnosis of RA, CD or UC, AS, PsO or PsA. As such, the study results may not be generalizable to pediatric patients, or those patients with no prior diagnosis of RA, CD or UC, AS, PsO or PsA.

# 12. PROTECTION OF HUMAN SUBJECTS

As these studies do not qualify as human subjects research, Institutional Review Boards (IRBs) have determined that studies conducted in IBM CCAE and Optum DOD (New England IRB). The IQVIA datasets are exempt from study-specific IRB review.

Confidentiality of patient records will be always maintained. All study reports will contain aggregate data only and will not identify individual patients or physicians. At no time during the study will the sponsor receive patient identifying information except when it is required by regulations in case of reporting adverse events.

# 13. SAFETY DATA COLLECTION AND REPORTING

This study uses coded data that already exist in an electronic database. In this type of data source, the minimum criteria for reporting an adverse event (i.e., identifiable subject, identifiable reporter, a suspect product, and event) are not available, and adverse events are not reportable as individual case safety reports. The study results will be assessed for medically important results.

# 14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study uses coded data that already exist in an electronic database. In this type of data source, the minimum criteria for reporting an adverse event (i.e., identifiable subject, identifiable reporter, a suspect product, and event) are not available, and adverse events are not reportable as individual case safety reports. The study results will be assessed for medically important results.

Results of this study will be disseminated through presentations at scientific conferences and/or through peer-reviewed publications.

# 15. LIST OF TABLES AND FIGURES

# 16. APPENDIX

## 16.1. Cohort Concept Sets

This file can be used to find the standardized OMOP concepts, from the OMOP Vocabulary, which are used in the cohort definitions below. The attached file has a column titled “CONCEPT_SET_NAME”, that can be used to locate the concepts sets mentioned. Concept sets will be surrounded by single quotes in the cohort definitions below. For example, if you want to find the 'Crohn’s disease' concept set, just filter to that using the “CONCEPT_SET_NAME” field.

EPI_964_CONCEPT_SETS_2022.11.10.xlsx

## 16.2. Indication Cohorts

### *16.2.1. Crohn’s Disease & Ulcerative Colitis*

**Cohort Entry Events**

People enter the cohort when observing any of the following:

1. condition occurrences of 'Crohn’s disease'.
2. condition occurrences of 'Ulcerative colitis'.

Limit cohort entry events to the earliest event per person.

**Cohort Exit**

The person exits the cohort at the end of continuous observation.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

### *16.2.2. Ankylosing Spondylitis*

**Cohort Entry Events**

People enter the cohort when observing any of the following:

- condition occurrence of 'Ankylosing Spondylitis' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

**Cohort Exit**

The person exits the cohort at the end of continuous observation.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

### *16.2.3. Moderate to severe plaque psoriasis & Psoriatic arthritis*

**Cohort Entry Events**

People enter the cohort when observing any of the following:

1. condition occurrences of 'Plaque psoriasis'.
2. condition occurrences of 'Psoriatic arthritis (exclude mutilans)'.
3. condition occurrences of 'Arthropathy'; having at least 1 condition occurrence of 'Psoriasis', starting between 60 days before and 60 days after 'Arthropathy' start date.

Limit cohort entry events to the earliest event per person.

**Cohort Exit**

The person exits the cohort at the end of continuous observation.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

### *16.2.4. Rheumatoid Arthritis*

**Cohort Entry Events**

People enter the cohort when observing any of the following:

1. condition occurrence of 'Rheumatoid arthritis' for the first time in the person's history.
2. observation of 'Rheumatoid arthritis' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

**Cohort Exit**

The person exits the cohort at the end of continuous observation.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

## 16.3. Persistence Window and Surveillance Window

The persistence window is the period of tolerance that is allowed when constructing periods of persistent exposure. For example, a 30-day persistence window would allow for a gap between two prescriptions not exceeding 30 days over the number of days supplied or prescribed.

The surveillance window is used to calculate the cohort exit based on the end of a persistent exposure to a drug. It is the number of days added to the end of persistence exposure to a drug as an additional period of surveillance prior to cohort exit. Example, if you have a drug exposure that ends on January 1 and your surveillance window is 30 days, if another drug exposure for that same drug occurs during the surveillance window you will consider the exposure to continue without stop.

For illustrative purposes, see Figure 4. Person A has two drug exposures. The second is within the 90-day persistence window thus we assume persistent exposure. Finding no additional exposures, at the end of the second drug exposure we add a 90-day surveillance window that allows us to calculate the end date of the drug exposure. Person B has two drug exposures. The second is outside the 90-day persistence window thus we do not assume persistent exposure. Finding no drug exposures within the persistence window, we calculate the drug exposure end date using the 90-day surveillance window.

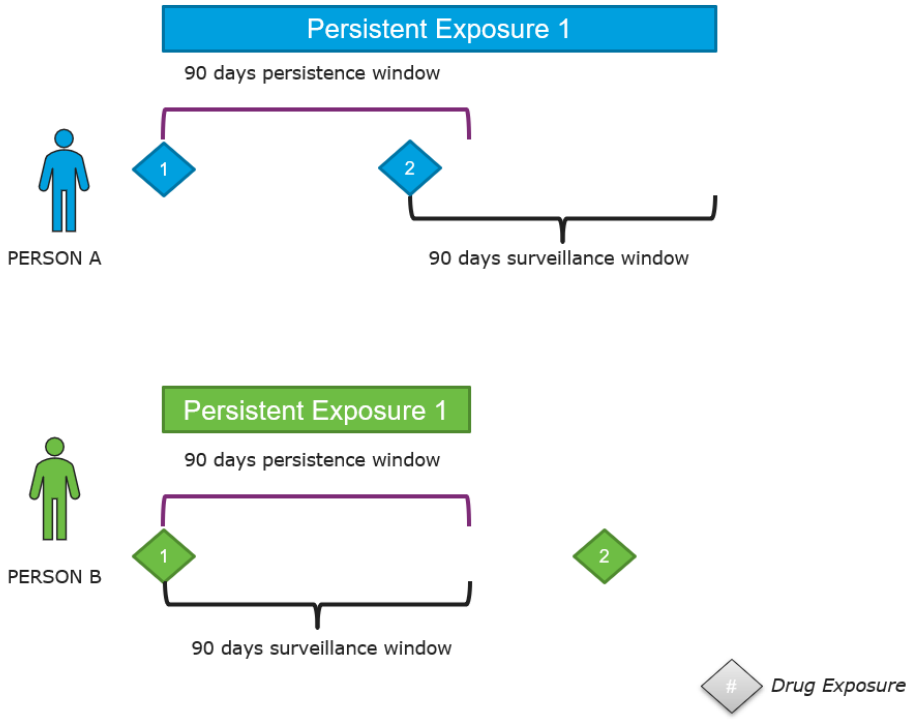


**Figure 4 – Example of the 90-day Persistence Window and 90-day Surveillance Window**

## 16.4. Target Cohorts

### *16.4.1. Remicade with CD/UC*

**Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of '[964] Infliximab (Remicade) plus source code' for the first time in the person's history, who are >= 18 years old; starting on or after August 24, 1998; having no drug exposures of '[964] Infliximab (all brands)', starting any time prior to '[964] Infliximab (Remicade) plus source code' start date.

Limit cohort entry events to the earliest event per person.

**Inclusion Criteria**

1. No prior other TNFai

   Entry events with all of the following criteria:

   a. having no drug exposures of '[964] adalimumab', starting anytime on or before cohort entry start date; allow events outside observation period.
   b. having no drug exposures of '[964] certolizumab pegol', starting anytime on or before cohort entry start date; allow events outside observation period.
   c. having no drug exposures of '[964] etanercept', starting anytime on or before cohort entry start date; allow events outside observation period.
   d. having no drug exposures of '[964] golimumab', starting anytime on or before cohort entry start date; allow events outside observation period.

2. No prior vedolizumab or natalizumab

   Entry events with all of the following criteria:

   a. having no drug exposures of '[964] vedolizumab', starting anytime on or before cohort entry start date; allow events outside observation period.
   b. having no drug exposures of '[964] natalizumab', starting anytime on or before cohort entry start date; allow events outside observation period.

3. No prior IL

   Entry events having no drug exposures of '[EPI_964] Interleukin inhibitors', starting anytime on or before cohort entry start date; allow events outside observation period.

**Cohort Exit**

The cohort end date will be based on a continuous exposure to '[964] Infliximab (Remicade) plus source code': allowing 90 days between exposures, adding 90 days after exposure ends, and forcing drug exposure days supply to: 1 day. The person exits the cohort when encountering any of the following events:

1. drug exposures of '[964] adalimumab'.
2. drug exposures of '[964] golimumab'.
3. drug exposures of '[964] certolizumab pegol'.
4. drug exposures of '[964] etanercept'.
5. drug exposures of '[EPI_964] Interleukin inhibitors'.
6. drug exposures of '[964] vedolizumab'.
7. drug exposures of '[964] natalizumab'.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

## *16.4.2. Remicade with AS*

**Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of '[964] Infliximab (Remicade) plus source code' for the first time in the person's history, who are >= 18 years old; starting on or after December 17, 2004; having no drug exposures of '[964] Infliximab (all brands)', starting any time prior to '[964] Infliximab (Remicade) plus source code' start date.

Limit cohort entry events to the earliest event per person.

**Inclusion Criteria**

1. No prior other TNFai

   Entry events with all of the following criteria:

   a. having no drug exposures of '[964] adalimumab', starting anytime on or before cohort entry start date; allow events outside observation period.
   b. having no drug exposures of '[964] certolizumab pegol', starting anytime on or before cohort entry start date; allow events outside observation period.
   c. having no drug exposures of '[964] etanercept', starting anytime on or before cohort entry start date; allow events outside observation period.
   d. having no drug exposures of '[964] golimumab', starting anytime on or before cohort entry start date; allow events outside observation period.
2. No prior IL

   Entry events having no drug exposures of '[EPI_964] Interleukin inhibitors', starting anytime on or before cohort entry start date; allow events outside observation period.

**Cohort Exit**

The cohort end date will be based on a continuous exposure to '[964] Infliximab (Remicade) plus source code': allowing 90 days between exposures, adding 90 days after exposure ends, and forcing drug exposure days supply to: 1 day. The person exits the cohort when encountering any of the following events:

1. drug exposures of '[964] adalimumab'.
2. drug exposures of '[964] golimumab'.
3. drug exposures of '[964] certolizumab pegol'.
4. drug exposures of '[964] etanercept'.
5. drug exposures of '[EPI_964] Interleukin inhibitors'.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

### *16.4.3. Remicade with PSO/PsA*

**Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of '[964] Infliximab (Remicade) plus source code' for the first time in the person's history, who are >= 18 years old; starting on or after May 13, 2005; having no drug exposures of '[964] Infliximab (all brands)', starting any time prior to '[964] Infliximab (Remicade) plus source code' start date.

Limit cohort entry events to the earliest event per person.

**Inclusion Criteria**

1. No prior other TNFai

   Entry events with all of the following criteria:

   a. having no drug exposures of '[964] adalimumab', starting anytime on or before cohort entry start date; allow events outside observation period.
   b. having no drug exposures of '[964] certolizumab pegol', starting anytime on or before cohort entry start date; allow events outside observation period.
   c. having no drug exposures of '[964] etanercept', starting anytime on or before cohort entry start date; allow events outside observation period.
   d. having no drug exposures of '[964] golimumab', starting anytime on or before cohort entry start date; allow events outside observation period.

2. No prior IL

   Entry events having no drug exposures of '[EPI_964] Interleukin inhibitors', starting anytime on or before cohort entry start date; allow events outside observation period.

**Cohort Exit**

The cohort end date will be based on a continuous exposure to '[964] Infliximab (Remicade) plus source code': allowing 90 days between exposures, adding 90 days after exposure ends, and forcing drug exposure days supply to: 1 day. The person exits the cohort when encountering any of the following events:

1. drug exposures of '[964] adalimumab'.
2. drug exposures of '[964] golimumab'.
3. drug exposures of '[964] certolizumab pegol'.
4. drug exposures of '[964] etanercept'.
5. drug exposures of '[EPI_964] Interleukin inhibitors'.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

### *16.4.4. Remicade and methotrexate with RA*

**Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of '[964] Infliximab (Remicade) plus source code' for the first time in the person's history, who are >= 18 years old; starting on or after November 10, 1999; with all of the following criteria:
    a. having no drug exposures of '[964] Infliximab (all brands)', starting any time prior to '[964] Infliximab (Remicade) plus source code' start date.
    b. having at least 1 drug exposure of '[964] methotrexate', starting between 30 days before and 30 days after '[964] Infliximab (Remicade) plus source code' start date.

Limit cohort entry events to the earliest event per person.

**Inclusion Criteria**

1. No prior other TNFai

    Entry events with all of the following criteria:

    1. having no drug exposures of '[964] adalimumab', starting anytime on or before cohort entry start date; allow events outside observation period.
    2. having no drug exposures of '[964] certolizumab pegol', starting anytime on or before cohort entry start date; allow events outside observation period.
    3. having no drug exposures of '[964] etanercept', starting anytime on or before cohort entry start date; allow events outside observation period.
    4. having no drug exposures of '[964] golimumab', starting anytime on or before cohort entry start date; allow events outside observation period.
2. No prior abatacept

    Entry events having no drug exposures of '[964] abatacept', starting anytime on or before cohort entry start date; allow events outside observation period.

3. No prior IL

    Entry events having no drug exposures of '[EPI_964] Interleukin inhibitors', starting anytime on or before cohort entry start date; allow events outside observation period.

**Cohort Exit**

The cohort end date will be based on a continuous exposure to '[964] Infliximab (Remicade) plus source code': allowing 90 days between exposures, adding 90 days after exposure ends, and forcing drug exposure days supply to: 1 day. The person exits the cohort when encountering any of the following events:

1. drug exposures of '[964] adalimumab'.
2. drug exposures of '[964] etanercept'.
3. drug exposures of '[964] golimumab'.

4. drug exposures of '[964] certolizumab pegol'.
5. drug exposures of '[EPI_964] Interleukin inhibitors'.
6. drug exposures of '[964] abatacept'.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

## 16.5. Comparator Cohorts

### *16.5.1. golimumab, certolizumab pegol, ustekinumab, vedolizumab with CD/UC*

**Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of '[964] golimumab, certolizumab pegol, ustekinumab, vedolizumab' for the first time in the person's history, who are >= 18 years old; starting on or after April 22, 2008.

Limit cohort entry events to the earliest event per person.

**Inclusion Criteria**

1. No prior other TNFai

   Entry events with all of the following criteria:

   a. having no drug exposures of '[964] Infliximab (all brands)', starting anytime on or before cohort entry start date; allow events outside observation period.
   b. having no drug exposures of '[964] adalimumab', starting anytime on or before cohort entry start date; allow events outside observation period.
   c. having no drug exposures of '[964] etanercept', starting anytime on or before cohort entry start date; allow events outside observation period.
2. No prior natalizumab

   Entry events having no drug exposures of '[964] natalizumab', starting anytime on or before cohort entry start date; allow events outside observation period.

3. No prior other IL

   Entry events having no drug exposures of '[EPI_964] Interleukin inhibitors', starting anytime on or before cohort entry start date; allow events outside observation period.

**Cohort Exit**

The cohort end date will be based on a continuous exposure to '[964] golimumab, certolizumab pegol, ustekinumab, vedolizumab': allowing 90 days between exposures, adding 90 days after exposure ends, and forcing drug exposure days supply to: 1 day. The person exits the cohort when encountering any of the following events:

1. drug exposures of '[964] Infliximab (all brands)'.
2. drug exposures of '[964] adalimumab'.
3. drug exposures of '[964] etanercept'.
4. drug exposures of '[EPI_964] Interleukin inhibitors'.
5. drug exposures of '[964] natalizumab'.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

### *16.5.2. certolizumab pegol, golimumab, ixekizumab, secukinumab with AS*

**Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of '[964] certolizumab pegol, golimumab, ixekizumab, secukinumab' for the first time in the person's history, who are >= 18 years old; starting on or after April 24, 2009.

Limit cohort entry events to the earliest event per person.

**Inclusion Criteria**

1. No prior other TNFai

   Entry events with all of the following criteria:

   1. having no drug exposures of '[964] Infliximab (all brands)', starting anytime on or before cohort entry start date; allow events outside observation period.
   2. having no drug exposures of '[964] adalimumab', starting anytime on or before cohort entry start date; allow events outside observation period.
   3. having no drug exposures of '[964] etanercept', starting anytime on or before cohort entry start date; allow events outside observation period.
2. No prior other IL

   Entry events having no drug exposures of '[EPI_964] Interleukin inhibitors', starting anytime on or before cohort entry start date; allow events outside observation period.

**Cohort Exit**

The cohort end date will be based on a continuous exposure to '[964] certolizumab pegol, golimumab, ixekizumab, secukinumab': allowing 90 days between exposures, adding 90 days after exposure ends, and forcing drug exposure days supply to: 1 day. The person exits the cohort when encountering any of the following events:

1. drug exposures of '[964] Infliximab (all brands)'.
2. drug exposures of '[964] adalimumab'.
3. drug exposures of '[EPI_964] Interleukin inhibitors'.

4. drug exposures of '[964] etanercept'.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

### *16.5.3. golimumab, certolizumab pegol, guselkumab, risankizumab, tildrakizumab, brodalumab, ixekizumab, secukinumab, or ustekinumab with PSO/PsA*

**Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of '[964] golim, certoliz, guselk, risankiz, tildrakiz, brodal, ixekiz, secukin, ustekin' for the first time in the person's history, who are >= 18 years old; starting on or after April 24, 2009.

Limit cohort entry events to the earliest event per person.

**Inclusion Criteria**

1. 1. No prior other TNFai

   Entry events with all of the following criteria:

   1. having no drug exposures of '[964] Infliximab (all brands)', starting anytime on or before cohort entry start date; allow events outside observation period.
   2. having no drug exposures of '[964] adalimumab', starting anytime on or before cohort entry start date; allow events outside observation period.
   3. having no drug exposures of '[964] etanercept', starting anytime on or before cohort entry start date; allow events outside observation period.
2. No prior other IL

   Entry events having no drug exposures of '[EPI_964] Interleukin inhibitors', starting anytime on or before cohort entry start date; allow events outside observation period.

**Cohort Exit**

The cohort end date will be based on a continuous exposure to '[964] golim, certoliz, guselk, risankiz, tildrakiz, brodal, ixekiz, secukin, ustekin': allowing 90 days between exposures, adding 90 days after exposure ends, and forcing drug exposure days supply to: 1 day. The person exits the cohort when encountering any of the following events:

1. drug exposures of '[964] Infliximab (all brands)'.
2. drug exposures of '[964] adalimumab'.
3. drug exposures of '[EPI_964] Interleukin inhibitors'.
4. drug exposures of '[964] etanercept'.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

### *16.5.4. certolizumab pegol, tocilizumab with RA*

**Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of '[964] certolizumab pegol, tocilizumab' for the first time in the person's history, who are >= 18 years old; starting on or after May 13, 2009.

Limit cohort entry events to the earliest event per person.

**Inclusion Criteria**

1. 1. No prior other TNFai

   Entry events with all of the following criteria:

   1. having no drug exposures of '[964] Infliximab (all brands)', starting anytime on or before cohort entry start date; allow events outside observation period.
   2. having no drug exposures of '[964] etanercept', starting anytime on or before cohort entry start date; allow events outside observation period.
   3. having no drug exposures of '[964] adalimumab', starting anytime on or before cohort entry start date; allow events outside observation period.
   4. having no drug exposures of '[964] golimumab', starting anytime on or before cohort entry start date; allow events outside observation period.
2. No prior abatacept

   Entry events having no drug exposures of '[964] abatacept', starting anytime on or before cohort entry start date; allow events outside observation period.

3. No prior other IL

   Entry events having no drug exposures of '[EPI_964] Interleukin inhibitors', starting anytime on or before cohort entry start date; allow events outside observation period.

**Cohort Exit**

The cohort end date will be based on a continuous exposure to '[964] certolizumab pegol, tocilizumab': allowing 90 days between exposures, adding 90 days after exposure ends, and forcing drug exposure days supply to: 1 day. The person exits the cohort when encountering any of the following events:

1. drug exposures of '[964] Infliximab (all brands)'.
2. drug exposures of '[964] adalimumab'.
3. drug exposures of '[964] golimumab'.
4. drug exposures of '[EPI_964] Interleukin inhibitors'.
5. drug exposures of '[964] abatacept'.

6. drug exposures of '[964] etanercept'.

## 16.6. Outcome Cohort

### *16.6.1. Non-infectious uveitis or iridocyclitis*

**Cohort Entry Events**

People enter the cohort when observing any of the following:

1. condition occurrence of 'Non-infectious uveitis or iridocyclitis' for the first time in the person's history; having at least 1 condition occurrence of 'Non-infectious uveitis or iridocyclitis', starting between 31 days after and 365 days after 'Non-infectious uveitis or iridocyclitis' start date.
2. condition occurrences of 'Non-infectious uveitis or iridocyclitis'; having at least 1 visit occurrence of any visit, starting anytime on or before 'Non-infectious uveitis or iridocyclitis' start date and ending between 0 days after and all days after 'Non-infectious uveitis or iridocyclitis' start date; a provider specialty that is: "ophthalmology", "retina ophthalmology", "glaucoma ophthalmology", "pediatric ophthalmology and strabismus", "cornea and external ophthalmology", "pediatric ophthalmology", "neuro-ophthalmology", "uveitis and ocular inflammatory disease ophthalmology" or "orthoptics".

Limit cohort entry events to the earliest event per person.

**Cohort Exit**

The person exits the cohort at the end of continuous observation.

**Cohort Eras**

Entry events will be combined into cohort eras if they are within 0 days of each other.

## 16.7. Negative Controls List

The following is a list of outcomes not believed to be caused by the exposures of interest.

## 16.8. Covariates Excluded from the Propensity Score Models

Below contains a list of all concepts that were excluded from the propensity score models.

| Table 7 - Covariates Excluded from the Propensity Score Models | |
|---|---|
| **Concept ID** | **Concept Name** |
| 21601421 | ANTIMETABOLITES |
| 21601386 | ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS |
| 1592513 | brodalumab |
| 912263 | certolizumab pegol |
| 2314231 | Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure) |
| 2314229 | Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug |
| 45889779 | Chemotherapy administration, subcutaneous or intramuscular |
| 21601195 | Electrolyte solutions |
| 21601422 | Folic acid analogues |
| 19041065 | golimumab |
| 1593700 | guselkumab |
| 21603891 | IMMUNOSUPPRESSANTS |
| 21603890 | IMMUNOSUPPRESSANTS |
| 937368 | infliximab |
| 21603914 | Interleukin inhibitors |
| 45888764 | Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug) |
| 21601194 | I.V. SOLUTION ADDITIVES |
| 21601153 | I.V. SOLUTIONS |
| 35603563 | ixekizumab |
| 1305058 | methotrexate |
| 21600857 | MINERAL SUPPLEMENTS |
| 21600884 | OTHER MINERAL SUPPLEMENTS |
| 4203722 | Patient encounter procedure |
| 1511348 | risankizumab |
| 21601179 | Salt solutions |
| 45892883 | secukinumab |
| 21603892 | Selective immunosuppressants |
| 21600885 | Sodium |
| 967823 | sodium chloride |
| 21601160 | Solutions affecting the electrolyte balance |
| 2314216 | Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of a new substance/drug (List separately in addition to code for primary procedure) |
| 35200139 | tildrakizumab |
| 40171288 | tocilizumab |
| 40161532 | ustekinumab |
| 45774639 | vedolizumab |

## 16.9. Full Diagnostics Results

The attachment contains full diagnostic results for all 80 database-analysis-comparison combinations. And analysis that received a 4 in “diagnosticsPassed” column, passed all 4 study diagnostics criteria and can be unblinded.

diagnosticsResults_ 2022.11.10.xlsx

## 16.10. Distributions of time between subsequent exposures for the study drugs

**Table 8 - Exposure date to next exposure date distributions in days for study drug exposure records**

| Database | Exposure name | Records | Mean | Std. Dev. | Min | p10 | p25 | p50 | p75 | p90 | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CCAE | certolizumab pegol | 256231 | 39.6 | 50.3 | 1 | 22 | 26 | 30 | 37 | 70 | 3525 |
| | golimumab | 217030 | 46.9 | 59.0 | 1 | 25 | 28 | 34 | 57 | 81 | 3654 |
| | guselkumab | 36948 | 62.8 | 44.5 | 1 | 37 | 49 | 56 | 65 | 85 | 1025 |
| | infliximab | 1716962 | 54.4 | 72.3 | 1 | 28 | 43 | 52 | 56 | 66 | 6733 |
| | infliximab | 1716962 | 54.4 | 72.3 | 1 | 28 | 43 | 51 | 57 | 65 | 6733 |
| | Remicade | 107258 | 56.6 | 65.1 | 1 | 29 | 41 | 52 | 62 | 79 | 4222 |
| | secukinumab | 199690 | 39.0 | 40.7 | 1 | 22 | 25 | 29 | 38 | 69 | 1714 |
| | ustekinumab | 259800 | 81.0 | 74.9 | 1 | 28 | 51 | 77 | 93 | 117 | 3232 |
| | vedolizumab | 158616 | 48.5 | 37.4 | 1 | 25 | 28 | 55 | 57 | 64 | 1839 |
| Optum EHR | certolizumab pegol | 132724 | 64.2 | 135.1 | 1 | 5 | 14 | 28 | 63 | 145 | 3419 |
| | golimumab | 103972 | 67.9 | 133.6 | 1 | 4 | 15 | 36 | 65 | 143 | 3785 |
| | guselkumab | 18077 | 71.7 | 104.2 | 1 | 6 | 15 | 44 | 82 | 175 | 3813 |
| | infliximab | 1047419 | 55.3 | 137.4 | 1 | 3 | 14 | 38 | 57 | 74 | 4855 |
| | infliximab | 1047419 | 55.3 | 137.4 | 1 | 4 | 14 | 38 | 56 | 73 | 4855 |
| | Remicade | 831118 | 62.7 | 153.1 | 1 | 6 | 15 | 39 | 56 | 93 | 4867 |
| | secukinumab | 114350 | 58.5 | 94.8 | 1 | 4 | 14 | 28 | 66 | 138 | 2317 |
| | ustekinumab | 167901 | 79.1 | 143.1 | 1 | 4 | 13 | 40 | 91 | 181 | 3886 |
| | vedolizumab | 162656 | 44.5 | 79.8 | 1 | 4 | 12 | 29 | 56 | 64 | 3187 |
| Optum DOD | certolizumab pegol | 238101 | 37.1 | 61.6 | 1 | 22 | 27 | 30 | 35 | 52 | 4469 |
| | golimumab | 175961 | 44.1 | 73.9 | 1 | 24 | 29 | 33 | 54 | 62 | 4051 |
| | guselkumab | 28617 | 62.8 | 47.5 | 1 | 37 | 46 | 56 | 66 | 89 | 1037 |
| | infliximab | 1029840 | 58.4 | 124.8 | 1 | 29 | 43 | 54 | 56 | 67 | 6732 |
| | infliximab | 1029840 | 58.4 | 124.8 | 1 | 29 | 43 | 54 | 56 | 67 | 6732 |
| | Remicade | 409159 | 60.6 | 114.6 | 1 | 28 | 43 | 54 | 57 | 71 | 5236 |
| | secukinumab | 144707 | 35.2 | 38.2 | 1 | 22 | 24 | 28 | 36 | 49 | 1859 |
| | ustekinumab | 162133 | 83.3 | 101.5 | 1 | 30 | 50 | 75 | 92 | 117 | 3813 |
| | vedolizumab | 113102 | 49.5 | 47.0 | 1 | 26 | 28 | 56 | 56 | 62 | 1993 |

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