Optum

Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data

Draft 2 EMA Protocol

Prepared for Eli Lilly and Company

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Protocol I6T-MC-B004

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Post-Authorisation Safety Study (PASS) Information

Title	Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data
Study Identifier	I6T-MC-B004
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EU PAS Register No:	EUPAS105671
Active Substance	Immunosuppressants, interleukin inhibitors, ATC code: L04AC24
Medicinal Product(s)	Omvoh™ (active substance: mirikizumab)
Product Reference	Marketing Authorisation Numbers: EU/1/23/1736/001 to 006
Procedure Number	EMEA/H/C/005122/0000
Marketing Authorisation Holder(s)	Eli Lilly Nederland B.V.
Joint PASS	No
Research Question and Objectives	Mirikizumab is an interleukin-23 (IL-23) antagonist that is approved by the United States Food and Drug Administration for the treatment of moderately to severely active ulcerative colitis (UC) among adults and authorized by the European Commission for the treatment of adult patients with UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment. Given that the long-term safety of mirikizumab exposure among patients with UC in routine clinical practice has not been fully characterized, an observational study will be conducted to: • Determine the incidence of severe liver injury (specifically severe acute liver injury [SALI]), serious and opportunistic infections, malignancies excluding non-melanoma skin cancer (NMSC), and major adverse cardiovascular events (MACE) among adult patients 18 years of age and older with a diagnosis of UC who are exposed to mirikizumab. • Determine the incidence of severe liver injury (specifically SALI), serious and opportunistic infections, malignancies excluding NMSC, and MACE among adult patients 18 years of age and older with a diagnosis of UC who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC in real world clinical practice in the US. Potential comparator medications include: o anti-tumour necrosis factor (anti-TNF) monoclonal antibodies (mAB) – adalimumab, golimumab, and infliximab o IL-12/23 inhibitor – ustekinumab o α4β7 integrin inhibitor – vedolizumab, and o sphingosine-1-phosphate (S1P) receptor modulators – ozanimod, etrasimod • Determine the incidence of the study outcomes among elderly patients 65 years of age and older.

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	• Estimate the hazard ratio for SALI, serious and opportunistic infections, malignancies excluding NMSC, and MACE among adult patients 18 years of age and older with a diagnosis of UC who are exposed to mirikizumab versus their propensity score (PS)-matched comparators (anti-TNF mABs, ustekinumab, vedolizumab, S1P receptor modulators) using Cox proportional hazards models. The analyses for this objective will be conducted if sufficient person-time accrual to detect a minimum relative risk of at least 1.5 to 2.5, depending on the outcome, at 80% power for each study outcome is attained.
Country(ies) of study	United States of America
Author(s)	PPD PPD Optum Epidemiology PPD PPD Optum Epidemiology PPD PPD Optum Epidemiology PPD PPD Eli Lilly and Company PPD PPD Eli Lilly and Company

Abbreviations: No = number; PAS = Post-Authorisation Study; PASS = Post-Authorisation Safety Study.

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Marketing Authorisation Holder

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2. List of Abbreviations

Term	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AE	adverse event
AZA	azathioprine
BMI	body mass index
CI	confidence interval
CMS	Centers for Medicare and Medicaid Services
COVID-19	coronavirus disease 2019
CPT®	Current Procedural Terminology
CV	cardiovascular
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS	European Union post-authorisation study
FDA	United States Food and Drug Administration
HBV	Hepatitis B virus
HCPCS	Healthcare Common Procedure Coding System
HCV	Hepatitis C virus
HR	hazard ratio
ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision

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ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICSR	Individual Case Safety Report
IL	interleukin
IPTW	inverse probability of treatment weighting
IRB	institutional review board
IV	intravenous
JAK	Janus kinase
K-M	Kaplan-Meier
mAB	monoclonal antibody
MACE	major adverse cardiovascular event
MA-PD	Medicare Advantage and Medicare Part D
MI	myocardial infarction
NASH	nonalcoholic steatohepatitis
NDC	National Drug Code
NDI	National Death Index
NMSC	non-melanoma skin cancer
ORD	Optum Research Database
PBRER	periodic benefit risk evaluation report
PH	proportional hazards
PPV	positive predictive value
PS	propensity score
PSUR	periodic safety update report
PSC	primary sclerosing cholangitis
PVAN	polyomavirus-associated nephropathy

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RMP	risk management plan
RR	relative risk
S1P	sphingosine-1-phosphate
SALI	severe acute liver injury
SSA	Social Security Administration
SAP	Statistical Analysis Plan
SC	subcutaneous
SOP	standard operating procedure
TNF	tumour necrosis factor
UC	ulcerative colitis
US	United States

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3. Responsible Parties

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4. Abstract

- Title: Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data
- Rationale and background: Mirikizumab is an interleukin-23 (IL-23) antagonist that was approved on 26 October 2023 for the treatment of moderately to severely active ulcerative colitis (UC) in adults by the United States (US) Food and Drug Administration (FDA) and authorized on 26 May 2023 by the European Commission for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment. The long-term safety of mirikizumab exposure among patients with UC in routine clinical practice has not been fully characterized. Eli Lilly and Company made a commitment to both the European Medicines Agency (EMA) and the US FDA to conduct an observational secondary database study to assess the long-term safety of mirikizumab in routine clinical practice using US administrative claims data.
- Research question and objectives: The goal of this study is to evaluate the long-term safety of mirikizumab and further characterize outcomes considered important potential risks. Specifically, the objectives of this study are to:
    - Determine the incidence of severe liver injury (specifically severe acute liver injury [SALI]), serious and opportunistic infections, malignancies excluding non-melanoma skin cancer (NMSC), and major adverse cardiovascular events (MACE) among adult patients 18 years of age and older with a diagnosis of UC who are exposed to mirikizumab.
    - Determine the incidence of severe liver injury (specifically SALI), serious and opportunistic infections, malignancies excluding NMSC, and MACE among adult patients 18 years of age and older with a diagnosis of UC who are not exposed to mirikizumab, and/or who are exposed to other medications that are indicated for the treatment of moderately to severely active UC in real world clinical practice in the US. Potential comparator medications include:
        - antitumour necrosis factor (anti-TNF) monoclonal antibodies (mABs) – adalimumab , golimumab, and infliximab
        - IL-12/23 inhibitor – ustekinumab
        - α4β7 integrin inhibitor – vedolizumab, and
        - sphingosine-1-phosphate (S1P) receptor modulators – ozanimod, etrasimod
    - Determine the incidence of the study outcomes among elderly patients 65 years of age and older.
    - Estimate the hazard ratio (HR) for SALI, serious and opportunistic infections, malignancies excluding NMSC, and MACE among adult patients 18 years of age and older with a diagnosis of UC who are exposed to mirikizumab versus their propensity score (PS)-matched comparators (anti-TNF mABs, ustekinumab, vedolizumab, S1P receptor modulators) using Cox proportional hazards (PH) models. The analyses for this objective will be conducted if sufficient person-time accrual to detect a minimum

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relative risk (RR) of at least 1.5 to 2.5, depending on the outcome, at 80% power for each study outcome is attained.

- Study design: This is an observational cohort study with a prevalent new user design that will use secondary data from an administrative claims database in the US. Study accrual starts on 26 October 2023, the date of mirikizumab approval for UC in the US, and follow-up will end in December 2036.
- Population: The source population will consist of patients with UC who have a dispensing of mirikizumab or any of the comparator medications on or after the start of study accrual. Consistent with the prevalent new user design, each patient in the source population who initiates mirikizumab, regardless of previous use of comparator medication, will enter the mirikizumab cohort at the date of first mirikizumab dispensing (index date) after the study accrual start. Each mirikizumab patient will be matched to up to 3 patients treated with anti-TNF mABs, 3 patients treated with ustekinumab, 3 patients treated with vedolizumab, and 3 patients treated with S1P receptor modulators with similar treatment histories using time-conditional PS-matching. Patients will be eligible for inclusion in this study if they are aged 18 years or older on their index date as defined in Section 9.2.5; have a diagnosis of UC any time prior to and including their index date; and have complete medical coverage and pharmacy benefits with at least 6 months of continuous health plan enrolment prior to and including their index date.
- Variables:

  Exposures:

  Exposure to mirikizumab and the comparator medications (adalimumab, golimumab, infliximab, vedolizumab, ustekinumab, ozanimod, and etrasimod) will be defined by the presence of National Drug Codes (NDCs) on pharmacy claims or Healthcare Common Procedure Coding System (HCPCS) codes on medical claims. Janus kinase inhibitors will not be considered as a comparator group, as these medications have been associated with an increased risk of MACE and malignancy, which may lead to potential channelling bias and/or confounding by indication.

  Outcomes:

  The study outcomes to be identified are (i) MACE, comprised of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular (CV) death (as defined in Section 9.3.4.1); (ii) all malignancies excluding NMSC (Section 9.3.4.2); (iii) serious and opportunistic infections (Section 9.3.4.3); and (iv) SALI, including toxic liver disease (except for alcoholic liver disease), hepatic failure (except for chronic or alcohol-induced), inflammatory liver disease (except for abscesses of the liver, phlebitis of the portal vein, and non-alcoholic steatohepatitis), central haemorrhagic necrosis of the liver, hepatic veno-occlusive disease, peliosis hepatis, and hepatorenal syndrome (Section 9.3.4.4). Study outcomes will be identified through claims indicators using published validated claims-based algorithms where available. The outcome of SALI will be validated using medical record review, and CV death will be identified using mortality data from the Social Security Administration (SSA) Death Master File, Centers for Medicare and Medicaid Services (CMS) death data, obituary data, and from patient discharge status

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indicators from facility claims, along with claims for CV conditions immediately preceding death. In the final analysis, a National Death Index (NDI) search will provide an additional source for the identification of CV death.

Covariates:

Baseline covariates will include information related to patient demographics, medical history of UC, history of UC treatment, history of selected chronic diseases, procedures and medications, and healthcare utilization. In addition, empirical predictors will be identified by examining the most frequently occurring diagnoses, drugs dispensed, and procedures performed among UC patients with and without a mirikizumab dispensing. Baseline covariates will be assessed in the 6 months prior to and including the index date, except for history of UC diagnosis or treatment, history of chronic diseases, and endpoint-specific exclusion criteria, which will be assessed using all available data up to 5 years prior to and including the index date (unless otherwise specified).This will help ensure capture of information in the secondary data that may not be present in claims on or immediately preceding the index date.

- Data sources: The study will be conducted using the Optum Research Database (ORD) and the Medicare Advantage and Medicare Part D (MA-PD) data. The ORD is a proprietary research database containing pharmacy and medical claims data from a large US health plan affiliated with Optum, Inc. For 2021, data are available for approximately 12.6 million individuals with medical and pharmacy coverage. The MA-PD data contain complete medical and pharmacy information for Medicare enrolees with medical and Medicare Part D coverage beginning in 2006. For 2021, data are available for approximately 7 million individuals with both medical and pharmacy benefit coverage. Individuals in the ORD are covered by a commercial health plan typically available through an employer, while those in the MA-PD are covered by a government-sponsored health plan only available to individuals aged 65 years or older or those with a qualifying disability. As such, individuals are not expected to appear in both the ORD and MA-PD databases in the same period of time, though they can move between databases over time. The individuals covered by these health plans are geographically diverse across the US. The ORD and MA-PD contain mortality data through linkages to the SSA death files, CMS death data, obituary data, and from patient discharge status indicators from facility claims. In addition, mortality data will be supplemented with linkages to the NDI.

- Study size: As mirikizumab is only recently on the market in the US, projections are based on market uptake of ustekinumab, an IL-12/23 agent indicated for moderately to severely active UC. From 2017 to 2022, 3490 patients with UC initiated ustekinumab, or approximately 582 patients per year. On average, patients diagnosed with UC were enrolled for 37.5 months (standard deviation [SD] 22.3 months), with a mean of 22.6 months (SD 18.9 months) from the UC diagnosis to disenrollment. Based on these numbers, approximately 5000 mirikizumab initiators are estimated to accrue during the roughly 10-year duration of this study. If each initiator contributes, conservatively, 1 person-year of follow-up, we expect 5000 person-years of follow-up. If 5000 person-years of follow-up are observed among mirikizumab users at a 3:1 ratio of comparator patients to mirikizumab initiators for each pairwise comparison (mirikizumab versus anti-TNF mABs, mirikizumab versus ustekinumab, mirikizumab versus vedolizumab, and

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mirikizumab versus S1P receptor modulators), the study is estimated to have 80% or greater power to detect the following minimum magnitudes of the RR: 1.75 for MACE, malignancies, and serious and opportunistic infections, assuming incidence rates of 523, 457.5, and 880 per 100,000 person-years, respectively; and for SALI, a RR of 1.5 to 2.5, based on incidence rates ranging from 1.4 to 18.9 per 1000 person-years.

- Data analysis: Conditional logistic regression models will be used to calculate the propensity for receiving mirikizumab, versus receiving (1) anti-TNF mABs, (2) ustekinumab, (3) vedolizumab, or (4) S1P receptor modulators, as a function of the time-varying patient characteristics measured at the point of the exposure set. In addition to adjusting for dispensing-based exposure sets, conditional logistic regression models will also adjust for patient characteristics identified *a priori* as potential risk factors for the study outcomes (that is, the covariates in Section 9.3.5). As there are 4 study outcomes, each with its own set of potential risk factors (Section 9.3.5) and outcome-specific exclusion criteria (Section 9.2.4), the propensity for receiving mirikizumab versus each of the 4 comparator treatments will be calculated as a function of the specific risk factors of each outcome, among only those patients who qualify for inclusion (that is, patients remaining after the application of the outcome-specific exclusion criteria). The resulting time-conditional PS will be used to identify 3 patients within each exposure set with the closest PS to that of the mirikizumab patient, creating 4 matched cohorts for each study outcome: mirikizumab patients 1:3 matched to patients receiving anti-TNF mABs; mirikizumab patients 1:3 matched to patients receiving ustekinumab; mirikizumab patients 1:3 matched to patients receiving vedolizumab; and mirikizumab patients 1:3 matched to patients receiving S1P receptor modulators. These matched cohorts will be used to conduct all primary, secondary, and sensitivity analyses. Comparative analyses will be presented only for those study outcomes for which there is sufficient person-time accrual to detect a minimum RR of at least 1.5 to 2.5 at 80% power, depending on the outcome, and for which the PS-adjusted cohorts are found to be balanced; for all other outcomes, descriptive analyses based on the same study population as the comparative analyses will be presented. Comparative analyses will employ Cox PH models to estimate the HR of study outcomes in mirikizumab patients versus their matched comparators; all Cox PH models will utilize robust variance estimators to account for clustering within matched sets. The primary analysis will consist of an initial set of Cox PH models estimating the HR of each outcome associated with mirikizumab use versus use of each of other comparators (anti-TNF mABs, ustekinumab, vedolizumab, or S1P receptor modulators). For the long-latency outcome of malignancy, the primary analysis will not account for change in exposure during follow-up, but rather continue to follow patients as though they had not switched from their first index therapy as described in Section 9.2.7. For the shorter latency outcomes of MACE, serious and opportunistic infections, and SALI, the primary analysis will allow for patients who switch from a comparator to mirikizumab to be followed in the comparator cohort up to the point of the switch, and the mirikizumab cohort afterwards (Section 9.2.7). To account for the potential impact of this non-independence in the estimation of confidence

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intervals, bootstrap sampling will be conducted as a sensitivity analysis. In accordance with study objectives, the primary analysis will be repeated among the subset of patients aged 65 years or older. A secondary analysis will be performed for the malignancy outcome in which, similar to the primary analysis of the shorter latency outcomes, patients who switch from a comparator to mirikizumab will be followed in the comparator cohort up to the point of the switch, and the mirikizumab cohort afterwards. Moreover, follow-up will begin on the day following the index date, rather than 1 year later as was the case in the primary analysis (Section 9.2.7). For the MACE outcome, a secondary analysis will stratify by previous history of MACE as an alternative to excluding patients with prior MACE diagnoses. A sensitivity analysis will be conducted in which the primary analysis is repeated after restricting the study population to patients with a minimum of 12 months of continuous enrolment prior to and including the index date. Another sensitivity analysis will repeat the primary analysis for MACE, restricting to the subset of patients in the study population that can be linked with the NDI death data. As an additional sensitivity analysis for the malignancy outcome, the duration of exposure to mirikizumab (for the mirikizumab patients), and anti-TNF mABs, ustekinumab, vedolizumab, or S1P receptor modulators (for the respective comparator patients) will be estimated based on per-label dosing schedules. Another sensitivity analysis will repeat the primary analysis using inverse probability of treatment weighting instead of PS-matching. Lastly, a quantitative bias analysis will evaluate the impact of potential unmeasured or uncontrolled confounding by estimating the magnitude of confounding that would be necessary to fully explain the observed risk ratio. Primary and secondary analyses will be presented in the interim report if sample size allows, along with descriptive characteristics of the mirikizumab and comparator cohorts and Kaplan-Meier (K-M) curves of all outcomes. Primary and secondary analyses will also be presented in the final report if sample size allows, along with the results of the medical record adjudication process for SALI and the results of the NDI search for CV deaths. If sample size allows, the final report will also contain a set of revised comparative analyses limiting SALI and CV death to outcomes confirmed via adjudication (for SALI) and via NDI search (for death).

- Milestones: Although patient accrual starts on the date of mirikizumab approval in the US (26 October 2023), the planned start of data collection (that is, the first extraction of data from the database) will occur within 2 years of EMA approval (that is, by 26 May 2025). Planned completion date for the final study report is 31 December 2037 (the date the final report is due to the EMA).

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5. Amendments and Updates

Not applicable.

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6. Milestones

Milestone	Planned Date
Draft protocol submission	26 November 2023
Final protocol submission	26 May 2024
Start of data collection (that is, the first extraction of data from the database)	By 26 May 2025
Study progress report[a]	To be provided with the PSUR
Interim report submission	31 December 2030
End of data collection	31 December 2036
Registration in the EU PAS register	02 October 2023
Final report of study results submission	31 December 2037

Abbreviations: EU = European Union; PAS = Post-Authorisation Study; PSUR = periodic safety update report

[a] Study progress reports will be provided with the Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR).

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7. Rationale and Background

UC is an idiopathic chronic inflammatory disease of the colon and rectum characterized by a dysregulated immune response to gut flora, leading to inflammation of the mucosal surface (Ordas et al. 2012). In the US and Europe, incidence of UC ranges from 9 to 20 cases per 100,000 person-years, while prevalence ranges from 156 to 291 cases per 100,000 people (Stewénius et al. 1995; Björnsson and Jóhannsson 2000; Bernstein et al. 2006; Vind et al. 2006; Kappelman et al. 2007; Loftus et al. 2007; Herrinton et al. 2008; Manninen et al. 2010). The pattern of incidence has been described as bimodal, with onset peaking between ages 15 and 30 years and again between ages 50 and 70 years (Ordas et al. 2012).

Conventional therapy for UC includes 5-ASA-containing medications (sulfasalazine, mesalazine, balsalazide, and olsalazine); systemic and/or topical corticosteroids; and the immunomodulators AZA, 6-MP, cyclosporine, and methotrexate (Berends et al. 2019). However, a significant number of patients, in particular those with moderately to severely active UC, may not respond to these therapies. As of July 2023, the following biological therapies are authorized in the EU: anti-TNF mABs adalimumab (EMA 2022a), golimumab (EMA 2023d), and infliximab (EMA 2022b) as second-line therapy for moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Additionally, the α4β7 integrin inhibitor vedolizumab (EMA 2023a) is authorized for adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or an anti-TNF mAB. Developed more recently, the IL-12/23 mAB ustekinumab (EMA 2023e) is authorized for adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to conventional therapy or a biologic agent (for example, anti-TNF mABs or vedolizumab).

In the US, the FDA approved golimumab for the treatment of adult patients with moderately to severely active ulcerative colitis who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, AZA, or 6-MP (Simponi package insert, 2018); and infliximab for the treatment of adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy (Remicade package insert, 2021). Similarly, adalimumab, ustekinumab, and vedolizumab are approved for the treatment of adults with moderately to severely active UC, but without requiring that patients have an inadequate response to first-line therapy (Humira package insert, 2021; Entyvio package insert, 2022; Stelara package insert, 2023). However, some medical insurers in the US may impose this requirement prior to authorizing coverage (AHP 2023; Cigna 2023; UHC 2023a, 2023b).

In addition to biologics, advanced targeted therapies for moderately to severely active UC include small molecules such as the S1P receptor modulators ozanimod and etrasimod, and JAK receptor inhibitors tofacitinib and upadacitinib. These are authorized by the EMA for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent

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(EMA 2023b, 2023f, 2023g, 2024). Similarly, the FDA approved upadacitinib for the treatment of adult patients with moderately to severely active UC who have had an inadequate response or intolerance to anti-TNF agents, and ozanimod, etrasimod, and tofacitinib for adults with moderately to severely active UC (Rinvoq package insert, 2022; Zeposia package insert, 2023; Xeljanz package insert, 2018; Velsipity package insert, 2023). Ozanimod is considered to be generally well tolerated, with infection-related or cardiovascular adverse events (AEs) that are manageable or transient (Paik 2022). However, there is concern that JAK inhibitors elevate the risk of MACE and cancer compared to biologics (Ytterberg et al. 2022), possibly due to their unique mechanism of action. These medications inhibit JAK receptors, which play important roles in the regulation of many systems of the body, including the cardiovascular system; furthermore, unlike biologics, which target individual cytokines (that is, TNF-alpha, IL-12, IL-23), JAK inhibitors block a wide spectrum of cytokines that bind to JAK receptors to transmit both pro- and anti-inflammatory signals (Kotyla et al. 2020). In light of these concerns, the EMA released a special warning that patients aged 65 years and older, those at increased risk of MACE or malignancy, and current or previous long-term smokers should only be prescribed JAK inhibitors when there are no other treatment alternatives (Rinvoq summary of product characteristics). Similarly, in the US, FDA-approved labels for tofacitinib and upadacitinib contain black box warnings for malignancy, MACE, and thrombosis (Rinvoq package insert, 2022; Xeljanz package insert, 2018).

On 26 May 2023, the EMA authorized mirikizumab, a mAB that binds to and inhibits IL-23, for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or biologic treatment (EMA 2023c). However, the long-term safety of mirikizumab exposure among patients with UC in routine clinical practice has not been fully characterized. Eli Lilly and Company has made a commitment to both the EMA and the FDA to conduct an observational secondary database study to assess the long-term safety of mirikizumab in routine clinical practice using US administrative claims data. The goal of this safety study is to examine the incidence of severe liver injury, serious infections, including opportunistic infections, malignancies excluding NMSC, and MACE among patients with a diagnosis of UC who are exposed to mirikizumab compared to patients with a diagnosis of UC who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC in real world clinical practice in the US (Lilly 2023). For the purposes of this study, severe liver injury will refer to SALI, consistent with regulatory interest in acute liver conditions. Study accrual is planned to begin on 26 October 2023, the date of FDA approval of mirikizumab for UC.

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8. Research Question and Objectives

The goal of this study is to evaluate the long-term safety of mirikizumab and further characterize outcomes considered important potential risks by examining the incidence of severe liver injury, serious infections, including opportunistic infections, malignancies excluding NMSC, and MACE among patients with a diagnosis of UC who are exposed to mirikizumab and those patients with a diagnosis of UC who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC in real world clinical practice in the US.

The objectives of this study are to:

- Determine the incidence of severe liver injury (specifically SALI), serious and opportunistic infections, malignancies excluding NMSC, and MACE among adult patients 18 years of age and older with a diagnosis of UC who are exposed to mirikizumab.
- Determine the incidence of severe liver injury (specifically SALI), serious and opportunistic infections, malignancies excluding NMSC, and MACE among adult patients 18 years of age and older with a diagnosis of UC who are not exposed to mirikizumab, and/or who are exposed to other medications indicated for the treatment of moderately to severely active UC in real world clinical practice in the US. Potential comparator medications include:
    - anti-TNF mABs – adalimumab or biosimilar, golimumab, and infliximab or biosimilar
    - IL-12/23 inhibitor – ustekinumab or biosimilar
    - α4β7 integrin inhibitor – vedolizumab, and
    - S1P receptor modulators – ozanimod, etrasimod
- Determine the incidence of the study outcomes among elderly patients 65 years of age and older.
- Estimate the HR for SALI, serious and opportunistic infections, malignancies excluding NMSC, and MACE among adult patients 18 years of age and older with a diagnosis of UC who are exposed to mirikizumab versus their PS-matched comparators (anti-TNF mABs or biosimilar, ustekinumab or biosimilar, vedolizumab, S1P receptor modulators) using Cox PH models. The analyses for this objective will be conducted if sufficient person-time accrual to detect a minimum RR of at least 1.5 to 2.5, depending on the outcome, at 80% power for each study outcome is attained.

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9. Research Methods

9.1. Study Design

This observational cohort study will use secondary data from an administrative claims database in the US. Study accrual starts on 26 October 2023, the date of mirikizumab approval for UC in the US, and will end on 31 December 2036.

This study will employ a prevalent new user design. When studying the effects of a newly approved treatment compared to an existing standard treatment, limiting the study design to patients who are treatment-naïve to both drugs (incident new user design) would exclude the patients who switched to mirikizumab from other UC treatments, which could represent a significant number of patients and a clinically relevant subset (Suissa et al. 2017). The prevalent new user design allows for the inclusion of these individuals, expanding study sample size, and potentially broadening the study population for inference (Webster-Clark et al. 2021).

The goal of this study is to evaluate the long-term safety of mirikizumab and further characterize outcomes considered important potential risks by examining the incidence of severe liver injury, serious infections, including opportunistic infections, malignancies excluding NMSC, and MACE among patients with a diagnosis of UC who are exposed to mirikizumab. Comparative analyses of the HRs for the study outcomes between patients with a diagnosis of UC who are exposed to mirikizumab and/or those who are exposed to other medications indicated for the treatment of moderately to severely active UC will be presented only for those outcomes for which there is sufficient person-time accrual to detect a minimum RR of at least 1.5 to 2.5, depending on the outcome, at 80% power (Section 9.5.2).

9.2. Setting

9.2.1. Source Population

The source population will consist of patients with UC enrolled in the claims-based ORD and MA-PD with a dispensing of mirikizumab or a comparator drug on or after 26 October 2023 through 31 December 2036. The ORD and MA-PD are described in detail in Section 9.4.

Figure 1, adapted from Suissa et al. (2017), illustrates a hypothetical example of the envisioned source population containing 13 patients with UC, but with different histories of exposure to the medications of interest. In the envisioned source population, dispensing 1 corresponds to the first dispensing of mirikizumab or a comparator medication in a patient's claims history. In Figure 1, patients A, B, C, E, and G all receive mirikizumab; patients A and B do so at their first dispensing, patient C at the third dispensing, patient E at the fourth dispensing, and patient G at the sixth dispensing. Some mirikizumab patients also have a different pattern of comparator use prior to their initial mirikizumab dispensing. For example, patients A and B have no history of prior comparator use, as mirikizumab represents their first observed dispensing of any study medication. By contrast, patient C has an anti-TNF mAB as the first dispensing, followed by ustekinumab as the second, before switching to mirikizumab. Among patients who do not initiate mirikizumab, patient D receives an anti-TNF mAB at the first dispensing, followed by

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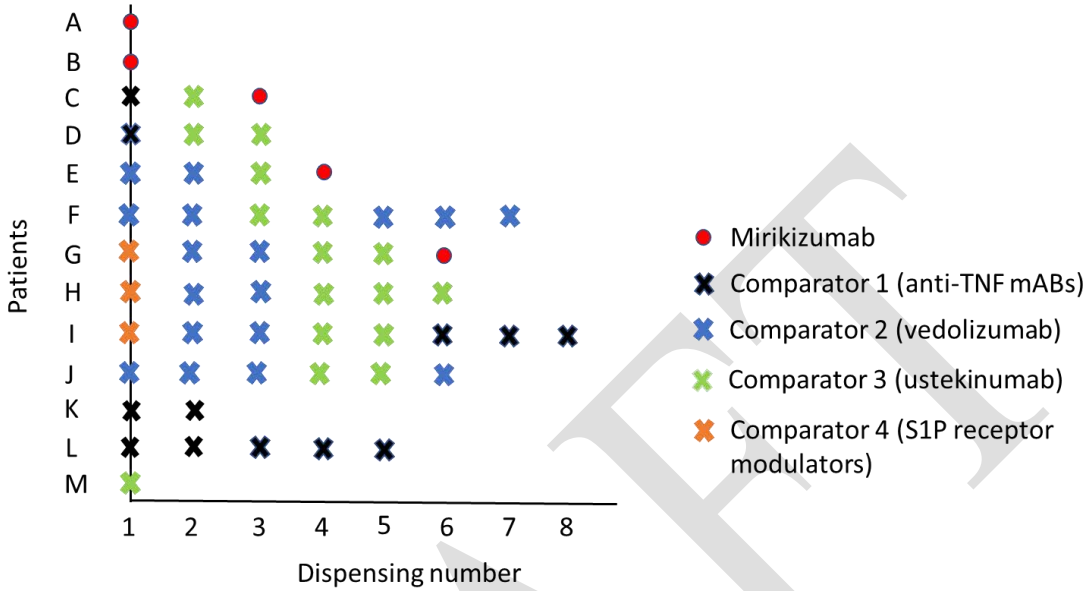
ustekinumab at the next 2 dispensings; patient F receives vedolizumab at the first 2 dispensings, ustekinumab at the next 2 dispensings, and vedolizumab at the next 3 dispensings; and so on.

Figure 1. Hypothetical source population.



Abbreviations: mAB = monoclonal antibody; S1P = sphingosine-1-phosphate; TNF = tumour necrosis factor.

Consistent with the prevalent new user design, each first instance of mirikizumab use in the source population will trigger the formation of a dispensing-based exposure set defined by the number and type of comparator drug prescriptions prior to the mirikizumab dispensing. For example, the hypothetical source population described above contains 4 exposure sets defined sequentially in time and marked by the red boxes in Figure 2. The exposure set defined at dispensing 1 (the earliest exposure set) contains all patients whose first dispensing is either mirikizumab or a comparator, that is, the entire source population. The exposure set defined at dispensing 3 (a later exposure set) contains members of the source population who received an anti-TNF mAB at their first dispensing and ustekinumab at their second dispensing, before receiving either mirikizumab or a comparator at their third dispensing (that is, patients C and D). The exposure set defined at dispensing 4 (an even later exposure set) contains members of the source population who received vedolizumab at their first and second dispensings, ustekinumab at their third dispensing, and either mirikizumab or a comparator at their fourth dispensing (that is, patients E and F). Finally, the exposure set defined at dispensing 6 (the latest exposure set) contains members of the source population who received an S1P receptor modulator at their first dispensing, vedolizumab at their second and third dispensings, ustekinumab at their fourth and fifth dispensing, and either mirikizumab or a comparator at their sixth dispensing (that is, patients G through I). The exposure sets will supply the study cohorts (Section 9.2.2), be used to define index dates (Section 9.2.5), and provide a pool of patients for the purposes of PS-matching (Section 9.7).

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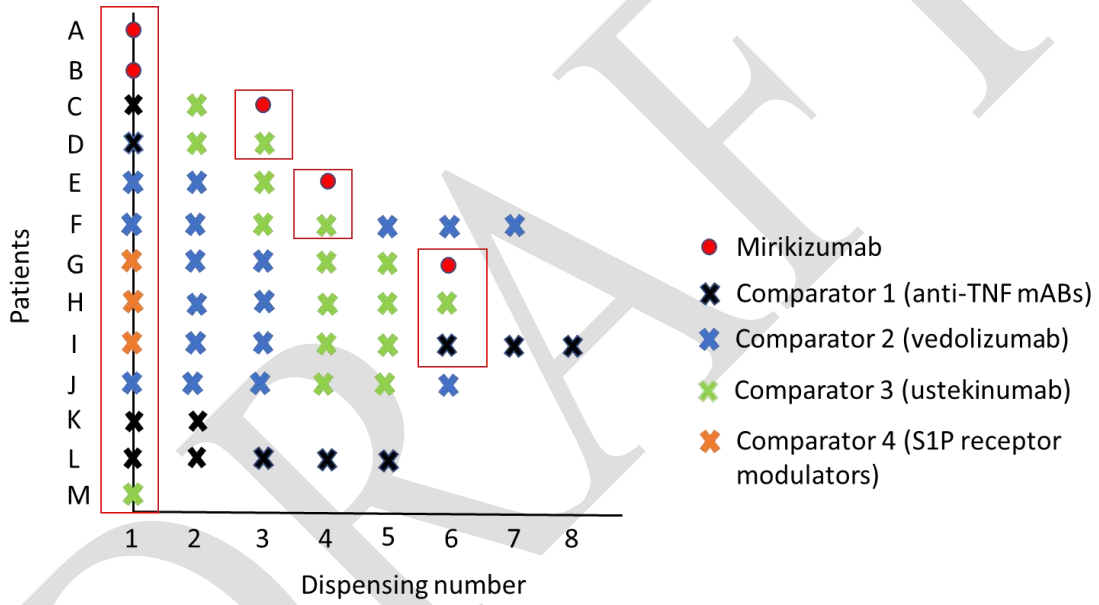
To the extent that the number of prior dispensings is a proxy for exposure time on each medication class, exposure sets based on the former also account for the latter. The choice to create exposure sets based on number of prior dispensings, rather than time on prior medication, reflects the fact that the former is directly captured in claims data, while the latter must be estimated based on quantities dispensed and per-label dosing schedules. However, if identifying exposure sets based on number and/or type of dispensings results in small sets and limited sample size, alternative definitions of medication history may be considered for defining exposure sets (for example, total time on each medication class).

Although the accrual period starts on the date of FDA approval of mirikizumab, treatment history that will be used to create the exposure sets will include dispensings that occur during baseline, including time prior to mirikizumab approval.

Figure 2. Dispensing-based exposure sets in the source population.



Abbreviations: mAB = monoclonal antibody; S1P = sphingosine-1-phosphate; TNF = tumour necrosis factor.

9.2.2. Study Population

9.2.2.1. Mirikizumab Cohort

The mirikizumab cohort will consist of those members of the source population who meet the eligibility criteria (Sections 9.2.3 and 9.2.4.1) and have a dispensing of mirikizumab on or after the date of mirikizumab approval in the US through 31 December 2036. Patients with dispensings of other study medications (Section 9.3.3) prior to a mirikizumab dispensing (that is, patients C, E, and G in Figure 2) will be eligible for the mirikizumab cohort. Thus, the mirikizumab cohort is expected to accrue 2 types of mirikizumab initiators: those with no prior exposure to comparator medication (incident new users), and those with previous comparator therapy (prevalent new users).

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A patient who is selected into the mirikizumab cohort in an earlier exposure set but switches to a comparator medication in a later exposure set will not be considered for comparator selection in later exposure sets (that is, will not be allowed to switch cohorts). However, the patient will be treated differently depending on the analysis of interest. In the primary analysis for the long-latency outcome of malignancy (Section 9.7.3.1), this patient will be considered a mirikizumab patient for the duration of the study. By contrast, in the primary analyses for the shorter-latency outcomes of MACE, serious and opportunistic infections, and SALI (Section 9.7.3.1), as well as in the secondary analysis of the malignancy outcome (Section 9.7.3.2), this patient will remain in the mirikizumab cohort until the point of switch and be dropped from the analysis thereafter (Suissa et al. 2017). Section 9.2.7 describes how this patient's follow-up will be handled in each analysis.

9.2.2.2. Comparator Cohorts

Since mirikizumab is indicated for the treatment of moderately to severely active UC, comparator medications of interest will include only those similarly indicated for moderately to severely active UC: the anti-TNF mABs adalimumab, golimumab, and infliximab, considered together because there is evidence that long-term safety outcomes (that is, malignancies, serious infections) are similar in this group (Humira package insert, 2021; Remicade package insert, 2021; Simponi package insert, 2018); the α4β7 integrin inhibitor vedolizumab; the IL-12/23 mAB ustekinumab; and the small molecule S1P receptor modulators ozanimod and etrasimod. JAK inhibitors will not be included because these medications have been associated with an increased risk of MACE and malignancy, which may lead to potential channelling and/or indication bias.

Based on the study medications of interest, 4 individual comparator cohorts will be created: the anti-TNF mAB cohort, comprised of users of adalimumab, golimumab, or infliximab; the vedolizumab cohort; the ustekinumab cohort; and the S1P receptor modulator cohort. Selection into the comparator cohorts will proceed as follows: for each mirikizumab user in a given exposure set, up to 3 patients will be selected for inclusion in each comparator cohort. Comparator patients will be selected from among members of the same exposure set who are not treated with mirikizumab. For example, in the hypothetical scenario depicted by Figure 2, comparator patients for mirikizumab users A and B would be selected from the remaining patients in the dispensing 1 exposure set; comparator patients for mirikizumab users C and E would be selected from the remaining patients in their respective exposure sets (patients D and F, respectively), and comparator patients for mirikizumab user G would be selected from patients H and I. If there are insufficient numbers of patients in many exposure sets, treatment history may be collapsed or categorized (for example, fewer than 5 anti-TNF mAB dispensings treated as a type of history). If a patient is selected into a comparator cohort in an earlier exposure set, he or she will no longer be considered for selection as a potential comparator in subsequent exposure sets (Suissa et al. 2017).

Comparator selection will be based on time-conditional PS-matching (Section 9.7), such that for each comparator cohort, the 3 patients with the same or closest PS as the mirikizumab user in a given exposure set will be selected (Suissa et al. 2017). To avoid selection bias, the identification

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of matched comparators will be performed in chronological order, with the first new user of mirikizumab in calendar time matched first to a comparator, the second new user of mirikizumab next, and so on. This will ensure that patient exclusions, such as a prior history of the outcome (Section 9.2.4), are applied starting from the exposure set of relevance (Suissa et al. 2017).

Finally, a patient who is selected as a comparator in an earlier exposure set but switches to mirikizumab in a later exposure set will be treated differently depending on the analysis of interest. In the primary analysis of the long-latency outcome of malignancy (Section 9.7.3.1), this patient will not be allowed to enter the mirikizumab cohort in the later exposure set (that is, will not be allowed to switch) but will be treated as a comparator for the duration of the study. By contrast, in the primary analysis of all other outcomes (Section 9.7.3.1), as well as in the secondary analysis of the malignancy outcome (Section 9.7.3.2), this patient will remain in the comparator cohort until the point of switch and enter the mirikizumab cohort thereafter, subject to continued eligibility per Sections 9.2.3 and 9.2.4.1 (Suissa et al. 2017). Section 9.2.7 describes how this patient's follow-up will be handled in each analysis.

9.2.3. Inclusion Criteria

To be eligible for the study, patients will be required to fulfil the following criteria:

- Be aged 18 years or older on the index date (Section 9.2.5)
- Have at least 6 months of continuous health plan enrolment with medical and pharmacy benefit coverage in the database prior to and including the index date (to establish baseline characteristics); and
- Have evidence of UC (Section 9.3.1) recorded on or prior to the index date.

For the purposes of ascertaining eligibility, evidence of UC will be ascertained based on all available information in the secondary data up to 5 years prior to and including the index date (Section 9.2.6).

9.2.4. Exclusion Criteria

9.2.4.1. General Exclusion Criteria

In order to only include patients among whom study medications (for example, infliximab) were prescribed for UC, patients will be excluded from all cohorts if they have other indications for the study medications prior to the index date (Section 9.2.5) (Kirchgesner et al. 2022). For the purposes of this exclusion, prior indications will be assessed using all available data up to 5 years prior to and including the index date to ensure capture of information in the secondary data regarding comorbidities that may not be present in claims on the index date. A single ICD-10-CM diagnosis code will be utilized to identify relevant non-UC indications. For example, patients will be excluded if they have any diagnosis code related to Crohn's disease (ICD-10-CM code K50.--), Rheumatoid arthritis (ICD-10-CM codes M05.-- and M06.--), Ankylosing spondylitis (ICD-10-CM code M45.--), Psoriatic arthritis (ICD-10-CM code L40.52), or Psoriasis (ICD-10-CM code L40.--) up to 5 years prior to and including their index date; the full list will be provided in the SAP and reviewed periodically, as some drugs may acquire new indications over time. If excluding patients based on a single ICD-10-CM code

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for a non-UC indication results in comparator cohorts with fewer than 3 matched comparators per mirikizumab patient, the use of validated algorithms to more precisely identify relevant non-UC indications will be considered. Candidate validated algorithms will be proposed in the SAP.

Individuals who have been exposed to JAK inhibitors prior to the index date will be excluded as these medications have been associated with an increased risk of MACE and malignancy, which may lead to potential channelling bias and/or confounding by indication.

9.2.4.2. Outcome-Specific Additional Exclusion Criteria

Additional exclusion criteria will be applied when creating the analytic population for each study outcome. Unless otherwise specified, outcome-specific exclusion criteria will be evaluated using all available data up to 5 years prior to and including the index date (Section 9.2.5). Definitions of prior MACE, infection, SALI, and malignancy will be consistent with outcome definitions as described in Section 9.3.4.

For analysis of the MACE outcome (as a composite and for each individual component):

- Any diagnosis of a MACE component prior to and including the index date.

For analysis of the infection outcome:

- Any serious infection occurring prior to and including the index date.
- Any opportunistic infection occurring in the 6 months prior to and including the index date.

For analysis of the SALI outcome:

- Any diagnosis of SALI occurring in the 6 months prior to and including the index date.
- Any hospitalization due to SALI prior to and including the index date.
- Predisposing factors prior to and including the index date: chronic liver disease, chronic pancreatic disease, alcohol abuse, intra- or extrahepatic biliary obstruction, primary or secondary hepatic, biliary, or pancreatic cancer, or metastatic cancer.
- Diagnosis of acute infectious hepatitis, acute cholelithiasis or cholecystitis, acute pancreatic disease, or acute congestive heart failure prior to and including the index date.

For analysis of the malignancy outcome:

- Malignancy diagnosis prior to and including the index date.

9.2.5. Index Date

For mirikizumab patients, the index date will be the date of first mirikizumab dispensing on or after the date of mirikizumab approval in the US. Each mirikizumab patient will have only 1 index date, coinciding with the dispensing date at which they received their first mirikizumab treatment. For example, in Figure 2, patient C received the first mirikizumab treatment after 2 dispensings of comparator medication. Thus, this patient's mirikizumab index date will be the date of the third dispensing.

For patients in the comparator cohorts, the index date will be tied to the dispensing-based exposure sets at which matching occurs. For example, in Figure 2, the hypothetical exposure set

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defined by dispensing 6 contains 2 possible comparators, patients H and I; assuming none were selected as comparators in earlier exposure sets (Section 9.2.2.2), all are eligible for comparator selection at dispensing 6. If, as a result of PS-matching, patient H is selected as a comparator, the index date for this patient will reflect the date at which he received his sixth drug dispensing, since this is the point at which he was matched to a mirikizumab patient.

9.2.6. Baseline Period

Per Section 9.2.3, patients will be required to have 6 months of continual medical and pharmacy coverage prior to and including the index date in order to be eligible for inclusion in the study. These 6 months (183 days) prior to and including the index date will constitute the minimum required baseline period in the primary analysis. For select patient characteristics, such as presence of UC and history of UC treatment, all available data up to 5 years prior to and including the index date will be used. The lookback period will be limited to 5 years based on the mean duration of enrolment among patients with UC in the databases (Section 9.5). Section 9.3.5 contains details on lookback periods for each individual covariate.

9.2.7. Follow-Up Period

The follow-up period will vary based on the outcome of interest and the analysis. In the primary analysis for the long-latency outcome of malignancy (Section 9.7.3.1), follow-up time for each cohort member will begin 1 year from the day following the index date to account for the long latency of some cancers, and will extend until a malignancy event, disenrollment from the health plan, death, or the end of data collection, whichever occurs first. This analysis will not account for change in exposure during follow-up.

In the primary analysis of all other outcomes (Section 9.7.3.1), as well as in the secondary analysis of the malignancy outcome (Section 9.7.3.2), follow-up time will extend from the day following the index date until an outcome of interest, a switch of the index treatment (for example, from a comparator to mirikizumab), UC surgery such as colectomy, disenrollment from the health plan, death, or end of data collection, whichever occurs first. Thus, a matched comparator who later switches to mirikizumab will be censored from the comparator cohort at the time of the switch and will subsequently contribute follow-up time to the mirikizumab cohort. By contrast, a mirikizumab patient who later switches to a comparator treatment will be censored at the time of the switch and cease to contribute follow-up thereafter as described in Section 9.2.2.1. Additionally, patients who switch from either mirikizumab or a comparator treatment to a JAK inhibitor will be censored at the time of the switch. Given the uncertain impact of reusing comparators who switch to mirikizumab, a sensitivity analysis using bootstrap sampling will be conducted to account for the potential impact of non-independence in the estimation of CIs (Suissa et al. 2017); details will be provided in the SAP.

The entirety of follow-up will be used to assess all study outcomes except for infections. To assess occurrence of infections, follow-up will extend from the day after the index date to 90 days after the treatment episode with the applicable study medication, in accordance with the published validated algorithm proposed to identify this outcome (Lo Re et al. 2021). A treatment episode will be defined according to the per-label dosing schedules and the half-lives of each

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medication of interest summarized in Section 9.3.2 and 9.3.3. For all other outcome algorithms, see Section 9.3.4.

9.3. Variables

Comprehensive lists of all variables, including exposures, outcomes, and covariates, will be detailed in the SAP.

9.3.1. Identification of Ulcerative Colitis

UC will be identified based on a single claim with an ICD-10-CM code for UC (K51.--) in addition to a dispensing of any of the study medications, all of which are indicated for adults with moderately to severely active UC (Section 9.2.2). Liu et al. (2009) developed a similar UC identification algorithm based on 1 ICD-9 code for UC and 1 dispensing of a UC-related drug (mesalamine, sulfasalazine, 6-mercaptopurine, azathioprine, methotrexate, glucocorticoids, or infliximab), and validated it in a US managed care system database against medical record review (PPV: 90%). However, because the Liu algorithm was based on ICD-9 codes and validated in a slightly different population (a managed-care network), and because the UC drugs included in the algorithm do not greatly overlap with the current study medications, the performance of this algorithm in the current study may differ. For this reason, alternate definitions of UC may be considered if additional validated, well-performing ICD-10 algorithms in US populations are published during the conduct of the study.

9.3.2. Use of Mirikizumab

Mirikizumab will be identified using NDCs and HCPCS codes as they become available. A detailed list of codes will be provided in the SAP.

The half-life of mirikizumab is approximately 9.3 days (EMA 2023c), and the dosing schedule in the US is as follows:

- Induction phase: 300 mg administered IV at Week 0, Week 4, and Week 8, and
- Maintenance phase: 200 mg administered by SC injection (given as 2 consecutive injections of 100 mg each) at Week 12, and every 4 weeks thereafter.

9.3.3. Use of Comparator Medications

Use of comparator medications will be identified through a combination of NDC and HCPCS codes. For concision, drugs with numerous NDC codes are here presented using generic names only. Half-lives and dosing schedules are also presented for use in determining treatment episodes (discussed in Section 9.2.7). NDC and HCPCS code lists will be provided in the SAP.

Adalimumab

- Adalimumab or biosimilar
- Generic drug name adalimumab, including but not limited to NDC codes for Humira™ and Anjevita™.
- Half-life (Humira package insert, 2012; Humira summary of product characteristics): approximately 14 days.

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- Dosing schedule (Humira package insert, 2012; Humira summary of product characteristics):
    - Induction: 160 mg on day 1 (or split over days 1 through 2), given as 4 injections of 40 mg in a single day or 2 injections of 40 mg per day on 2 consecutive days; 80 mg on day 15 (given as 2 injections of 40 mg per day), and
    - Maintenance: 40 mg every other week starting on Day 29 via SC injection.

Golimumab

- Generic drug name golimumab, including but not limited to NDC codes for Simponi™.
- Half-life (Simponi summary of product characteristics; Simponi package insert, 2013): approximately 14 days.
- Dosing schedule (Simponi summary of product characteristics; Simponi package insert, 2013):
    - Induction: 200 mg SC injection at Week 0, followed by 100 mg at Week 2, and
    - Maintenance: 100 mg every 4 weeks thereafter.

Infliximab

- Infliximab or biosimilar
- Generic drug name infliximab, including but not limited to NDC codes for Remicade™, Inflectra™, Renflexis™, and Avsola™.
- Half-life (Remicade summary of product characteristics): 8 to 9.5 days.
- Dosing schedule (Remicade summary of product characteristics; Remicade package insert, 2021):
    - Induction: 5 mg/kg IV infusion on Weeks 0, 2, and 6, and
    - Maintenance: 5 mg/kg IV infusion every 8 weeks thereafter.

Ustekinumab

- Ustekinumab or biosimilar
- Generic drug name ustekinumab, including but not limited to NDC codes for Stelara™.
- Half-life (Stelara summary of product characteristics; Stelara package insert, 2019): 19 days.
- Dosing schedule (Stelara summary of product characteristics; Stelara package insert, 2019):
    - Induction: a single IV infusion using weight-based dosage. For ≤55 kg, 260 mg (2 vials); for 55 kg to 85 kg, 390 mg (3 vials); for >85 kg, 520 mg (4 vials), and
    - Maintenance: 90 mg subcutaneous at Week 8, then every 12 weeks thereafter (increase to frequency of every 8 weeks if no response).

Vedolizumab

- Generic drug name vedolizumab, including but not limited to NDC codes for Entyvio™.
- Half-life (Entyvio summary of product characteristics; Entyvio package insert, 2014): approximately 25 days.

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- Dosing schedule (Entyvio summary of product characteristics; Entyvio package insert, 2014):
    - Induction: 300 mg IV infusion over approximately 30 minutes on Weeks 0, 2, and 6, and
    - Maintenance: 300 mg IV infusion every 8 weeks thereafter.

Ozanimod

- Generic drug name ozanimod, including but not limited to NDC codes for Zeposia™.
- Half-life (Zeposia package insert, 2023; Zeposia summary of product characteristics): approximately 21 hours.
- Dosing schedule (Zeposia package insert, 2023):
    - Days 1 to 4: 0.23 mg once daily
    - Days 5 to 7: 0.46 mg once daily, and
    - Day 8 and thereafter: 0.92 mg once daily, or 0.92 mg once every other day in patients with mild to moderate hepatic impairment.

Etrasimod

- Generic drug name etrasimod, including but not limited to NDC codes for Velsipity™.
- Half-life (Velsipity package insert, 2023; Velsipity summary of product characteristics): approximately 30 hours.
- Dosing schedule (Velsipity package insert, 2023):
    - 2 mg once daily.

9.3.4. Outcomes

The study outcomes of interest are:

- MACE, as a composite endpoint for each of the following individual clinical events:
    - non-fatal MI
    - non-fatal stroke
    - CV death
- Serious and opportunistic infections, comprising all serious infectious and parasitic diseases, except for sequelae of infections. This includes serious infections of COVID-19, and opportunistic infections (that is, tuberculosis, herpes zoster, and so on) (Section 9.3.4.3). Note that for the purposes of this study, serious infection refers to clinically severe infection leading to hospitalization (as defined in Section 9.3.4.3)
- All malignancies excluding NMSC, and
- SALI, including toxic liver disease (except for alcoholic liver disease), hepatic failure (except for chronic or alcohol-induced), inflammatory liver disease (except for abscesses of liver, phlebitis of the portal vein, and NASH), central haemorrhagic necrosis of the liver, hepatic veno-occlusive disease, peliosis hepatis, or hepatorenal syndrome.

These outcomes will be defined using published, validated, well-performing algorithms when possible (Sections 9.3.4.1 to 9.3.4.4). Only incident outcomes during follow-up will be evaluated; prevalent or recurrent outcomes will not be considered, and in fact are not likely given the outcome-specific exclusions in Section 9.2.4.2. Code lists for all outcomes are available upon request (Annex 1).

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9.3.4.1. Major Adverse Cardiovascular Event

Components of MACE will be identified using ICD-10 codes adapted from algorithms developed in a German claims population (Platzbecker et al. 2022). These algorithms define an acute MI as hospitalization with a main diagnosis of Acute MI (ICD-10: I21.- and I22.-); a stroke as hospitalization with a main diagnosis of Stroke classified as Ischemic (I63.-), Haemorrhagic (I61.-), or unspecified (I63.9); and a CV death as a combination of an indicator of death and, within 60 days before the death date, a hospitalization with a main diagnosis of Cardiac arrest (I46.-), Heart failure (I11.0, I13.0, I13.2, I50.-), Cardiac arrhythmia (I44.-, I47.-, I48.-, I49.-), Stroke (I61.-, I63.-), Cerebrovascular disease (G45.3. G45.8, G45.9), or Acute MI (I21.-, I22.-). The algorithm for acute MI yielded a PPV of 97.6%; that for Stroke, 94.8%; and that for CV death, 79.9% (Platzbecker et al. 2022).

While well-performing validated algorithms for various MACE components have been developed in US populations (Bosco et al. 2021), they reflect ICD-9 era diagnostic codes. Our proposed ICD-10 algorithms, though developed and validated using German data, are generally consistent with US-based ICD-9 era algorithms (Bosco et al. 2021; Cutrona et al. 2013; Solomon et al. 2016), as well as in alignment with consensus MI, CV death, and stroke definitions (Hicks et al. 2018). If well-performing ICD-10 algorithms validated with US data are published during the conduct of the study, they will be considered for inclusion into our MACE definition.

For CV death, mortality data (as described in Section 9.4.2), along with claims for cardiovascular conditions within 60 days before the death date, will be used to identify CV death in the full study population. In the final report, an NDI search will be used to provide an additional source for the identification of CV death (Holick et al. 2009).

9.3.4.2. Malignancies

Malignancies will be identified using the algorithm published by Webber et al. (2019), which was validated against medical records from the US Armed Forces Defense Medical Surveillance System. Developed for use in cancer surveillance, this algorithm aims to broadly detect any site-specific malignancy using ICD-9 or ICD-10 diagnostic codes by specifying 3 criteria by which malignancy codes may classify as cases: 1) a hospitalization with a diagnostic code for a malignancy in the primary diagnostic position (inpatient); 2) a hospitalization with a diagnostic code for a malignancy in the secondary diagnostic position and a therapeutic treatment V code in the primary position (inpatient plus therapy); or 3) 3 or more outpatient encounters within a 90-day period with a diagnostic code for a malignancy in the primary or secondary position (outpatient). When all 3 criteria were applied in tandem, the PPV for all malignant cancers was 78.8% (95% CI: 77.2–80.3). For the 12 cancer sites with at least 50 total cases captured by the algorithm, the PPV ranged from a high of 99.6% for cancer of the breast and cancer of the testis (95% CI: 97.8–100.0 and 97.7–100.0, respectively) to a low of 78.1% (95% CI: 71.3–83.9) for non-Hodgkin lymphoma. The PPVs for the individual algorithm criteria were 81.7% (95% CI: 79.3–83.9) for inpatient, 62.9% (95% CI: 50.5–74.1) for inpatient plus therapy, and 80.7% (95% CI: 79.1–82.2) for outpatient, with the outpatient criterion capturing the most confirmed cases (Webber et al. 2019).

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9.3.4.3. Serious and Opportunistic Infections

Serious infections will be identified using a validated claims-based algorithm developed by Lo Re et al. (2021) among US patients with inflammatory bowel disease, psoriasis, or rheumatological conditions who initiated therapy with a biologic agent. This algorithm requires a claim for a hospital admission with a discharge diagnosis of infection, preceded by an ICD-10 code for infection or a dispensing for an antimicrobial in the 7 days prior to hospitalization. This latter criterion is applied to increase the likelihood that the infection was acquired in an outpatient setting, as infections that develop in the outpatient setting and precipitate hospital admission are more likely to be due to preadmission exposure to drugs. This algorithm was validated against medical records and performed well, with a PPV of 80.2% (95% CI: 75.1–84.6) (Lo Re et al. 2021). However, the index infection was limited to bacteraemia, pneumonia, skin or soft tissue infection, gastrointestinal infection, osteomyelitis, pyelonephritis, and meningitis, so the list of infections may be expanded for the current study to include additional subtypes particularly relevant among patients with UC (for example, COVID-19). The final algorithm will be supplied in the SAP.

Opportunistic infections will comprise infections that occur as a result of immunosuppression, for example, within the setting of biologic therapy. Winthrop et al. (2015) performed a systematic review of published literature and created a consensus list of OIs in the setting of biologic therapy. Included in the list are:

- Pneumocystis jirovecii
- Paracoccidioides infections
- BK virus disease including PVAN
- Penicillium marneffei
- Cytomegalovirus disease
- Sporothrix schenckii
- Post-transplant lymphoproliferative disorder
- Cryptosporidium species (chronic disease only)
- Progressive multifocal leukoencephalopathy
- Microsporidiosis
- Bartonellosis (disseminated disease only)
- Leishmaniasis (visceral only)
- Blastomycosis
- Trypanosoma cruzi infection (Chagas' disease) (disseminated disease only)
- Toxoplasmosis
- Campylobacteriosis (invasive disease only)
- Coccidioidomycosis
- Shigellosis (invasive disease only)
- Histoplasmosis
- Vibriosis (invasive disease due to Vibrio vulnificus)
- Aspergillosis (invasive disease only)
- HCV progression
- Candidiasis (invasive disease or pharyngeal)

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- Cryptococcosis
- Other invasive fungi: Mucormycosis (zygomycosis) (Rhizopus, Mucor, and Lichtheimia), Scedosporium/Pseudallescheria boydii, Fusarium
- Legionellosis
- Listeria monocytogenes (invasive disease only)
- Tuberculosis
- Nocardiosis
- Non-tuberculous mycobacterium disease
- Salmonellosis (invasive disease only)
- HBV reactivation
- Herpes simplex (invasive disease only)
- Herpes zoster (any form), and
- Strongyloides (hyperinfection syndrome and disseminated forms only)

The definition of opportunistic infections in the current study will be based on the above list. Winthrop et al. (2015) did not report validated ICD-10-based algorithms for opportunistic infections; however, other validation studies have found that adding a requirement for a hospitalization and restricting to principal discharge diagnoses yields higher PPVs (Schneeweiss et al. 2007; Grijalva et al. 2008; Barber et al. 2013). Adding a requirement for an inpatient claim may be considered for some opportunistic infections (that is, tuberculosis), but will not be used for opportunistic infections that do not generally require hospitalization, such as herpetic infections (Hsu et al. 2019). For the latter, we will use 1 or more ICD-10-CM codes in conjunction with a suitable antimicrobial dispensing (King 2017) to establish presence of the outcome but may refine this approach if additional published well-performing claims-based algorithms become available during the course of the study.

9.3.4.4. Severe Acute Liver Injury

SALI will initially be identified using a single claim with a diagnosis code for liver injury, including toxic liver disease (except for alcoholic liver disease), hepatic failure (except for chronic or alcohol-induced), inflammatory liver disease (except for abscesses of liver, phlebitis of the portal vein and NASH), central haemorrhagic necrosis of the liver, hepatic veno-occlusive disease, peliosis hepatis, or hepatorenal syndrome. Since published validated algorithms for SALI have performed poorly (Lo Re et al. 2013), medical record review will be used to validate this outcome. For more information on the medical record procurement and adjudication process, see Section 9.3.4.5.

9.3.4.5. Procurement and Adjudication Process for Severe Acute Liver Injury

Medical record procurement will be undertaken to confirm the cases of SALI (Section 9.3.4.4). A chronological listing of relevant claims will be reviewed for each potential case in order to determine the medical site of treatment most likely to yield medical records with the necessary information to confirm case status. When procuring medical records to confirm outcomes that meet the criteria of the claims review process, Optum, in collaboration with a clinician(s), will develop a medical record review form that will include clinical elements necessary to confirm the outcome diagnosis. Providers will be asked to send all available medical information

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occurring during the period of interest (surrounding the service date of the relevant claim). This will include, but is not limited to:

- office visit notes
- history and physical exam reports
- laboratory reports
- diagnostic imaging reports
- hospital discharge summaries
- surgical reports
- histology/pathology reports, and
- consultation/specialist notes.

For each potential case, 1 medical record will be requested from 1 provider. Of those that are requested, approximately 70%–85% of the medical records are expected to be successfully obtained (Seeger 2006; Johannes 2007).

Optum will contract with and pay 3 clinical consultants to perform outcome adjudication. The clinical consultants will form an adjudication panel with 3 members. The panel will be made up of clinicians with expertise on liver injury and will perform outcome adjudication on the potential cases of SALI. The clinical consultants will be blinded to exposure to the medications of interest. Each medical record, in conjunction with the clinical profiles, will be reviewed independently by 2 clinical consultants from the panel to determine outcome status. In the case that the adjudication results are discrepant, the third clinical consultant from the panel will adjudicate, with the final case assignment to correspond with the majority opinion. Adjudication results, including PPVs evaluating the performance of the claims-based algorithm for SALI, will be presented in the final report (Section 9.7.3).

9.3.5. Covariates

Covariates assessed prior to and including the index date will be reported descriptively for each study cohort and also considered for inclusion into the PS analysis (Section 9.7.1). All covariates will be identified using diagnostic (that is, ICD-10-CM), procedure (that is, Current Procedural Terminology [CPT]®[1] and HCPCS) or medication (for example, NDC) codes. Code lists for all covariates are available upon request (Annex 1).

While all patients will be required to have at minimum 6 months of available baseline data, some patients may have available medical and pharmacy claims data looking back up to 5 years prior to and including their index date (Section 9.2.6). This presents an opportunity to identify certain chronic or persistent characteristics over a longer timeframe than the 6-month baseline period, allowing for more accurate capture of covariates given that some information, particularly for comorbidities, may not be present on medical and/or pharmacy claims on, or immediately

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preceding, the index date. Thus, while some covariates will be assessed at the index date or in the 6 months prior, others will be assessed using all available data up to 5 years prior. Moreover, while certain covariates will be assessed for all outcomes, others will be assessed for specific outcomes only. Covariates of interest and their assessment periods are listed for all outcomes in Section 9.3.5.1 and by outcome in Sections 9.3.5.2, 9.3.5.3, 9.3.5.4, and 9.3.5.5.

In assessing covariates using all available data prior to and including the index date, consideration must be given to the fact that the length of available pre-index time may vary patient-to-patient. Therefore, covariates included as counts may be adjusted for the amount of pre-index time observed. For instance, in addition to describing the total number of serious and opportunistic infections for each cohort prior to and including the index date, we may consider describing the number of infections in the 30 days prior to and including the index date and the average number of such infections per month. Similarly, in addition to describing the total number of dispensings of UC medication in each cohort pre-index, we might also consider describing the average number of dispensings per month.

No over-the-counter medications will be assessed due to the unavailability of this information in the database. Drug use and disease status will be categorized as yes (code present) or no (no code present). Covariates identified as potential confounding variables based on *a priori* knowledge (for example, expert opinion and literature reviews) will be considered for inclusion in the PS model, except for prior use of study medications (anti-TNF mABs, vedolizumab, ustekinumab, or S1P receptor modulators). These covariates will be described in patient characteristics tables and used in the creation of the exposure sets as outlined in Section 9.2.1. As available, published validated algorithms will be used to identify or refine the identification of key covariates (that is, diabetes). Additional predictors of receiving mirikizumab compared to other therapy will be identified on an empiric basis by examining the most frequently occurring diagnoses, drugs dispensed, and procedures performed among UC patients with and without a mirikizumab dispensing. Other claims-based covariates may be considered and added during the course of the study.

9.3.5.1. Covariates Assessed for All Outcomes

The following covariates will be reported descriptively for all outcomes and study cohorts and will also be considered for inclusion into all PS models. The decision to include covariates in the PS models will depend on whether they are deemed to be confounding variables based on *a priori* knowledge (that is, expert opinion and the clinical literature).

Assessed at index date:

- Demographics
  - Age
  - Sex
  - Geographic region (US Northeast, West, Midwest, South, Unknown)
- Payer type (Commercial, MA-PD)
- Year of index date

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Assessed in the 6 months prior to and including index date (minimum required baseline period):

- BMI (ICD-10-CM diagnostic codes are available for the following categories: ≤19.9, 20-29, 30-39, ≥40 kg/m^2)
- Obesity
- Medical services utilization
    - Number of outpatient visits
    - Number of physician visits
    - Number of emergency room visits
    - Number and length of stay of hospitalisations

Assessed up to 5 years prior to and including index date, as data allow:

- Length of health plan membership since the start of enrolment
- Prior use of first-line UC medications (total number of dispensings prior to and including the index date; average dose per dispensing; average dosing interval)
    - 5-ASA-containing medications
        - Sulfasalazine
        - Mesalazine
        - Balsalazide
        - Olsalazine
    - Corticosteroids
        - Prednisolone
        - Prednisone
        - Methylprednisolone
        - Budesonide
    - Immunomodulators
        - AZA
        - 6-MP
        - Cyclosporine
        - Methotrexate
- Prior use of later-line UC medications (total number of dispensings prior to and including the index date; average dose per dispensing; average dosing interval; number of dispensings identifiable as an induction dose; number of dispensings identifiable as a maintenance dose)
    - Second-line:
        - Anti-TNF mABs
            - Adalimumab or biosimilar
            - Golimumab
            - Infliximab or biosimilar
        - Vedolizumab
        - Ustekinumab or biosimilar
        - S1P receptor modulators
            - Etrasimod
            - Ozanimod

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9.3.5.2. Major Adverse Cardiovascular Event

The study cohorts created to evaluate the MACE outcome will exclude individuals with MACE events in the 5 years prior to and including the index date (Section 9.2.4.2). However, the following additional covariates related to cardiovascular risk will be assessed in these cohorts up to 5 years prior to and including the index date, as data allow:

- Diagnoses, procedures, and medications associated with an increased risk of cardiovascular disease
    - Diagnoses: hypertension, hyperlipidemia, dyslipidemia, atherosclerosis, unstable angina, ischemic heart disease, diabetes, peripheral vascular disease, smoking, and obesity.
    - Procedures: angioplasty and stents, coronary artery bypass graft, heart valve surgery, catheter ablation, implanted pacemakers and defibrillators, smoking-related interventions.
    - Medications that may modify the risk of cardiovascular events, such as antihypertensives, anti-arrhythmics, anti-hyperlipidemics, antiplatelet agents, or diabetes medications.
        - *Note:* these medications will be assessed during 2 separate periods: in the 6 months prior to and including the index date, and using all available data (up to 5 years) prior to and including the index date.

These covariates will be reported descriptively for each study cohort created for the MACE outcome and will also be considered for inclusion in the PS models that will be used to create the analytic populations for the MACE outcome.

9.3.5.3. Malignancies

The study cohorts created to evaluate the malignancy outcome will exclude individuals with malignancies (except for NMSC) in the 5 years prior to and including the index date (Section 9.2.4.2). However, the following additional covariates related to malignancy risk will be assessed in these cohorts up to 5 years prior to and including the index date, as data allow:

- Smoking
- Benign tumours
- Carcinoma in situ
- Myelodysplastic syndromes, and
- Polycythaemia vera.

9.3.5.4. Serious and Opportunistic Infections

The study cohorts created for the analysis of serious and opportunistic infections will exclude individuals with such infections prior to and including the index date (Section 9.2.4.2). However, the following additional covariates related to serious and opportunistic infections will be assessed in these cohorts up to 5 years prior to and including the index date, as data allow:

- Diagnoses, procedures, and medications associated with an increased risk of serious or opportunistic infection
    - Diagnoses: history of opportunistic infections from 5 years to 6 months prior to the index date (individuals with opportunistic infections during the 6-month

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period prior to and including the index date will be excluded per Section 9.2.4.2); human immunodeficiency virus; cardiac valve malformations and septum defects that may increase the risk of, for example, endocarditis
        - *Note*: serious infections (as defined in Section 9.3.4) occurring up to 5 years prior to and including the index date will not be assessed as covariates, since these are exclusion criteria for the study cohorts used in the infection analysis (Section 9.2.4.2).
    - Procedures: organ transplantation, open surgical procedures, procedures related to foreign body removal and artificial stoma
    - Medications: immunosuppressive medications, for example, corticosteroids, antibody-based therapies, costimulatory blockade (Roberts and Fishman 2020).
        - *Note:* because medications dispensed further back in time from the index date are less likely to modify the risk of serious or opportunistic infections, these medications will be assessed during 2 separate periods: in the 6 months prior to and including the index date, and using all available data (up to 5 years) prior to and including the index date.
- History of cancer, excluding NMSC, in the 6 months prior to and including the index date.

9.3.5.5. Severe Acute Liver Injury

The study cohorts created to evaluate the SALI outcome will exclude individuals with SALI events and predisposing factors in the 5 years prior to and including the index date (Section 9.2.4.2). However, the following additional covariates related to SALI risk will be assessed in these cohorts up to 5 years prior to and including the index date, as data allow:

- Diagnoses and medications associated with an increased risk of liver injury
    - Diagnoses: sepsis, congestive heart failure, vascular diseases that may cause liver failure (that is, Budd-Chiari syndrome), potential liver complications of UC such as PSC and primary biliary cirrhosis.
    - Medications (David and Hamilton 2010): flucloxacillin, acetaminophen, amoxicillin/clavulanic acid, phenytoin, valproic acid, isoniazid, ezetimibe, halothane, diclofenac, bromfenac, nimesulide, beta-lactams (penicillin, cephalosporins), macrodantin, sulfonamide, antifungals (ketoconazole and other azoles), terbinafine, highly active antiretroviral therapy (nevirapine), glimepiride.
        - *Note:* because medications dispensed further back in time from the index date are less likely to modify the risk of liver injury, these medications will be assessed during 2 separate periods: in the 6 months prior to and including the index date, and using all available data (up to 5 years) prior to and including the index date.

9.4. Data Sources

9.4.1. Optum Claims Data

9.4.1.1. Optum Research Database

The patients included in this study will be drawn from a proprietary research database containing pharmacy and medical claims data from a large US health plan affiliated with Optum. The

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individuals covered by this health plan are geographically diverse across the US. As early as 1993, medical and pharmacy claims data are available for 70 million individuals with both medical and pharmacy benefit coverage. For the year of 2021, data are available for approximately 12.6 million individuals with medical and pharmacy coverage. Optum research activities use de-identified data from the research database. In limited instances, patient identifiers may be accessed where applicable law allows the use of patient-identifiable data, and when the study obtains appropriate approvals for accessing data that are not de-identified.

9.4.1.2. Medicare Advantage and Medicare Part D Data

Medicare is a US government health insurance plan offered to individuals aged 65 or older, certain younger individuals with disabilities, and patients with end-stage renal disease. Beginning in 2006, complete medical and pharmacy information is available for Medicare enrolees with medical and Medicare Part D coverage. The pharmacy claims contain sufficient information to trace patients' pharmacy expenditures through the multiple phases of the Medicare Part D plans. For 2021, data are available for approximately 7 million individuals with both medical and pharmacy benefit coverage. The individuals covered by this health plan are geographically diverse across the country and fairly representative of the US Medicare population.

Although Optum research activities use de-identified data from MA-PD, in limited instances (that is, in order to seek medical records for the purposes of outcome adjudication), patient identifiers may be accessed where applicable law allows the use of patient-identifiable data, and when the study obtains appropriate approvals for accessing data that are not de-identified.

Individuals in the ORD are covered by a commercial health plan typically available through an employer, while those in the MA-PD are covered by a government-sponsored health plan only available to individuals aged 65 years or older or those with a qualifying disability. As such, individuals are not expected to appear in both the ORD and MA-PD databases at the same time, though they can move between databases over time.

For both the ORD and MA-PD, pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, billing information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications.

Medical and facility claims are accessible from all available healthcare sites (for example, inpatient hospital, outpatient hospital, emergency room, physician's office, and surgery centre) for nearly all types of provided services, including specialty, preventive, and office-based treatments. Medical claims include information such as diagnoses (ICD-10-CM since 01 October 2015), procedures (CPT®[2] and HCPCS), site of service, provider specialty, revenue codes, and paid amounts. The coding of medical claims conforms to insurance industry standards.

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Claims for ambulatory services submitted by individual providers, for example, physicians, use the HCFA-1500 or CMS-1500 formats. Claims for facility services submitted by institutions, for example, hospitals, use the UB-82, UB-92, UB-04, or CMS-1450 formats.

9.4.2. Supplemental Data Sources

9.4.2.1. National Death Index Database

The NDI database is a central computerized index of death record information comprised of data on file in the state vital statistics offices (CDC 2022). The National Center for Health Statistics maintains the database, which contains both date and cause of death for adults and children. Records from 1979 are available and contain a standard set of identifying information on each death. Death records are added to the NDI file annually, typically within 12 months after the end of a particular calendar year. Early release files for a particular calendar year will be available for NDI routine searches when approximately 90% of the year's death records have been received and processed, but no later than 6 months after the end of the calendar year. However, completion status may vary by state (70% to 100%) and the early release file is subject to additions and corrections. NDI data may be linked to a subset of the ORD (approximately 40%) or MA-PD (approximately 77%) databases following necessary approvals; this linkage will be performed to supplement deaths and cause of death data for the final report where possible. The NDI linkage will be enhanced (improving our ability to assess the matches between the NDI data and Optum's data) with data from complementary sources of death information (Section 9.4.2.2), which are available in the Optum claims data.

9.4.2.2. Non-National Death Index Mortality Data

Mortality information from the NDI linkage will be complemented by linkages to the SSA death files, CMS death data, obituary data, and from patient discharge status indicators from facility claims. The SSA, CMS, and obituary data are externally sourced, linked using unique identifiers and incorporated into the Optum claims database on a quarterly basis. Following necessary approvals, the SSA and CMS death information provide a date of death, while obituary data provides month and year of death. They do not include cause of death and have a lag of approximately 3 months.

9.5. Study Size

9.5.1. Preliminary Counts in Optum Data

Table 1 shows the total number of patients with 1 or more diagnostic codes for UC and/or a dispensing for a UC medication in the ORD and MA-PD data from 01 January 2017 through 31 October 2022. Table 2 shows the mean person-months of enrolment among patients with 1 or more diagnoses of UC in the same period. These counts are for informational purposes only. Final sample size for the study could change depending upon criteria applied during the conduct of the protocol and required approvals.

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Table 1. ORD and MA-PD Patients with ≥1 Diagnosis of UC and/or ≥1 UC Medication[a], 01 January 2017 through 31 October 2022

	2017	2018	2019	2020	2021	2022	Total[b]
Patients with ≥1 UC code	53,494	57,455	60,650	57,906	65,187	56,909	209,681
18-35 years	8585	8986	9068	8414	8639	7226	30,758
>35-50 years	11,589	12,041	12,111	11,296	11,877	9879	38,621
>50-65 years	15,790	16,217	17,053	15,674	17,425	13,969	59,098
>65-75 years	11,117	12,697	13,927	13,823	16,694	15,485	51,079
>75 years	6413	7514	8491	8699	10,552	10,350	30,125
UC *and* Adalimumab	2456	2633	2856	2683	2912	2507	9600
UC *and* Golimumab	334	304	290	219	228	192	874
UC *and* Infliximab	2977	3218	3191	3056	3219	2998	9773
UC *and* Ustekinumab	206	337	498	869	1385	1466	3490
UC *and* Vedolizumab	1469	1992	2618	3033	3482	3427	8491

Abbreviations: MA-PD = Medicare Advantage and Medicare Part D; ORD = Optum Research Database; UC = ulcerative colitis.

a Year refers to year of UC diagnosis. For the purposes of this informational count, medication dispensings can occur any time in the year of diagnosis, either prior to or following the UC diagnosis itself.

b Individuals appearing multiple years across the entire 2017-2022 period are only counted once.

Table 2. Mean Person-months of Enrolment Among ORD and MA-PD Patients with ≥1 Diagnosis of UC, 01 January 2017 through 31 October 2022

	Mean (SD) Person-months of Enrolment[a]	Mean (SD) Person-months from UC Diagnosis to Disenrollment[b]
Patients with ≥1 UC code	37.5 (22.3)	22.6 (18.9)
18-35 years	29.5 (20.6)	19.3 (17.2)
>35-50 years	34.6 (22.1)	22.3 (19.0)
>50-65 years	37.2 (22.0)	22.5 (18.6)
>65-75 years	41.9 (21.9)	25.1 (19.7)
>75 years	42.1 (22.6)	22.4 (19.1)

Abbreviations: MA-PD = Medicare Advantage and Medicare Part D; ORD = Optum Research Database; SD = standard deviation; UC = ulcerative colitis.

a Time from first enrolment into the ORD/MA-PD until disenrollment from the ORD/MA-PD.

b Time from first observed UC diagnosis in the ORD/MA-PD until disenrollment from the ORD/MA-PD.

Table 1 illustrates that between 2017 and 2022, there were 3490 unique users of ustekinumab in the ORD and MA-PD, or approximately 582 users per year. Assuming that mirikizumab users accrue into the study at the same rate, and further assuming that study accrual continues for 11 years (Section 6), we may accrue as many as 6402 mirikizumab users during the study period. A more conservative estimate might consider that mirikizumab uptake may be slower than that

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of ustekinumab (for instance, 500 users per year). Thus, conservatively there may be as many as 5000 mirikizumab new users accrued during the study. Table 2 suggests that the average UC patient has approximately 2 years (23 months) of enrolment after their UC diagnosis. If we consider that for mirikizumab users, follow-up cannot start until after mirikizumab is dispensed, we might conservatively estimate an average of at least 1 year of follow-up for each mirikizumab user. Thus, 5000 mirikizumab users accrued over the course of the study would contribute a total of 5000 person-years of follow-up.

9.5.2. Estimated Power

The power to detect a range of RRs based on person-years of mirikizumab exposure observed was calculated for each study outcome separately. These power calculations were performed to determine the sample size needed to detect an increased risk of study outcomes among mirikizumab users versus users of comparator treatments, if an increased risk is present. All calculations and associated graphics were produced using a Microsoft Excel-based tool developed by Optum Epidemiology based on established methods (Miettinen 1969; Rothman and Boice 1979).

9.5.2.1. Major Adverse Cardiovascular Event

Figure 3 shows the power of the study to detect a range of RR for the MACE outcome, up to the upper limit expected (5000 mirikizumab new users), assuming a 1:3 ratio of mirikizumab to comparators in each pairwise comparison (mirikizumab versus anti-TNF mABs, mirikizumab versus ustekinumab, mirikizumab versus vedolizumab, and mirikizumab versus S1P receptor modulators), a 2.3% incidence (risk not rate) of major cardiovascular events in the comparator group (Gill et al. 2021) and a 2-sided alpha level of 0.05. Converting the 2.3% risk to a rate based on the published study follow-up yields an incidence rate of 523 per 100,000 person-years for MACE. Accordingly, the study will have more than 80% power to detect a minimum RR of at least 1.75 for the outcome of MACE if 5000 mirikizumab person-years are observed and more than 80% power to detect a minimum RR of at least 2.0 if at least 3000 person-years of mirikizumab follow-up are observed.

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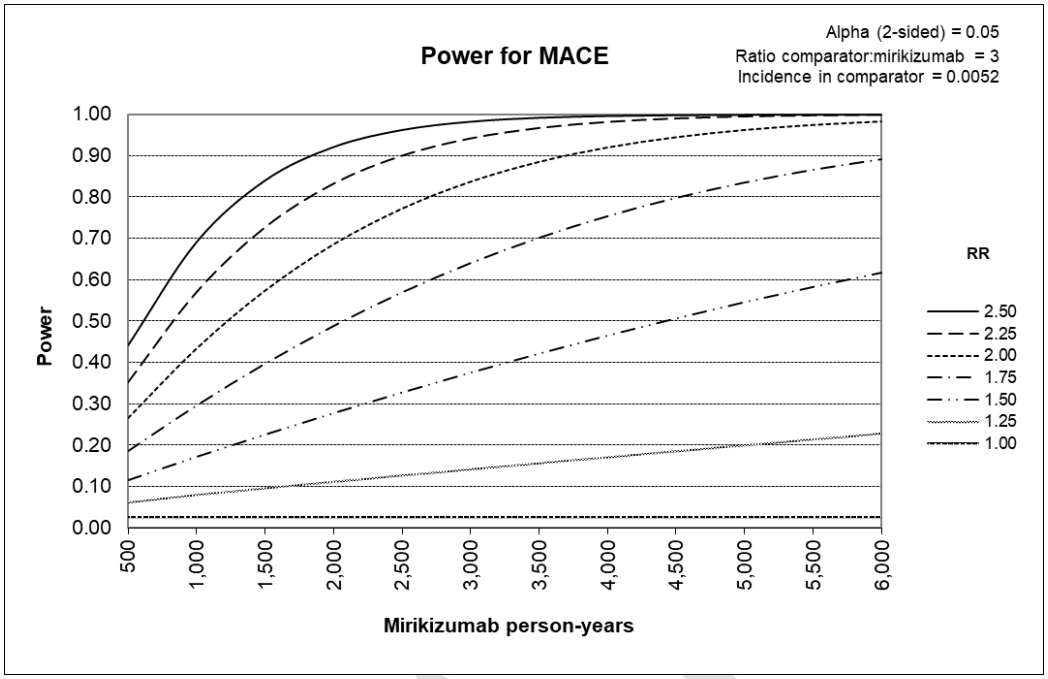
Figure 3. Power of the study to detect a range of relative risks for MACE.



Abbreviations: MACE = major adverse cardiovascular event; RR = relative risk.

While a matching ratio of 1:3 is the goal of the study, it may not be feasible for every mirikizumab patient. Therefore, Table 3 illustrates the power to detect a RR of 2.0 for MACE assuming a more conservative matching ratio of mirikizumab patients to comparators. Even under the most conservative matching ratio (1:1), the study will have more than 80% power to detect a RR of 2.0 if 5000 person-years of mirikizumab exposure are accrued.

Table 3. Power to Detect a Relative Risk of 2.0 for MACE[a] Under Alternate Assumptions

Mirikizumab:Comparator Ratio	Mirikizumab Person-years	Power to Detect RR of 2.0
1:1	3000	63.6%
	4000	76.6%
	5000	85.4%
	6000	91.2%
1:2	3000	78.7%
	4000	88.6%
	5000	94.1%
	6000	97.1%

Abbreviations: MACE = major adverse cardiovascular event; RR = relative risk.

[a] Assumes a 2-sided alpha level of 0.05 and an incidence rate of 523 per 100,000 person-years in the unexposed for MACE.

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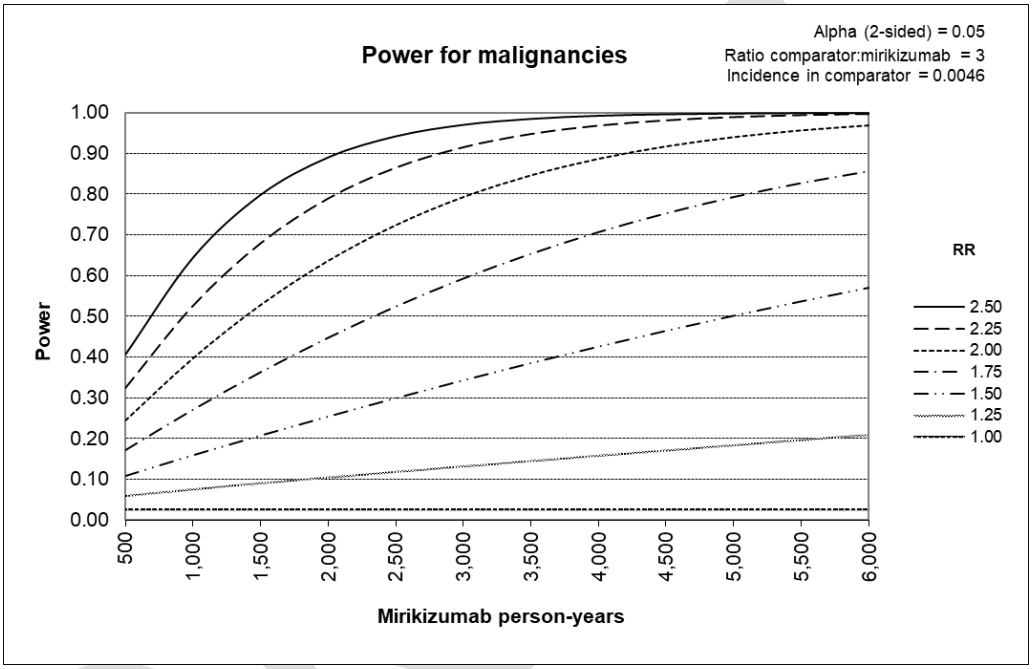
9.5.2.2. Malignancies

For other study outcomes, the power varies in relation to the expected incidence of the outcome. The power for malignancies (Figure 4) is based on an incidence rate of 457.5 per 100,000 person-years in the US, although the incidence rate in patients with UC may be somewhat higher (Hemminki et al. 2008; Cronin et al. 2022). We used general US population incidence estimates to be conservative, and the resulting power curves for malignancies are quite similar to those for MACE, providing for more than 80% power to detect a minimum RR of at least 1.75 with 5000 person-years or a minimum RR of at least 2.0 with 3000 mirikizumab person-years.

Figure 4. Power of the study to detect a range of relative risks for malignancies.



Abbreviation: RR = relative risk.

Table 4 illustrates the power to detect a minimum RR of at least 2.0 for malignancies assuming a more conservative matching ratio of mirikizumab to comparators in each pairwise comparison (mirikizumab versus anti-TNF mABs, mirikizumab versus ustekinumab, mirikizumab versus vedolizumab, and mirikizumab versus S1P receptor modulators). Even under the most conservative matching ratio (1:1), the study will have approximately 80% power to detect a minimum RR of at least 2.0 if 5000 person-years of mirikizumab are accrued.

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Table 4. Power to Detect a Relative Risk of 2.0 for Malignancies[a] Under Alternate Assumptions

Mirikizumab:Comparator Ratio	Mirikizumab Person-years	Power to Detect RR of 2.0
1:1	3000	57.8%
	4000	70.9%
	5000	80.5%
	6000	87.3%
1:2	3000	73.6%
	4000	84.5%
	5000	91.2%
	6000	95.1%

Abbreviation: RR = relative risk.

[a] Assumes a 2-sided alpha level of 0.05 and an incidence rate of 457.5 per 100,000 person-years in the unexposed for malignancies.

9.5.2.3. Serious and Opportunistic Infections

The incidence rate for serious and opportunistic infections has been estimated to be 880 per 100,000 person-years in UC patients unexposed to thiopurines and anti-TNFs (Kirchgesner et al. 2018). This incidence rate yields power curves that suggest the study will have more than 90% power to detect a minimum RR of at least 1.75 if 5000 person-years are observed and more than 80% power to detect a minimum RR of at least 2.0 if 2000 person-years are observed (Figure 5).

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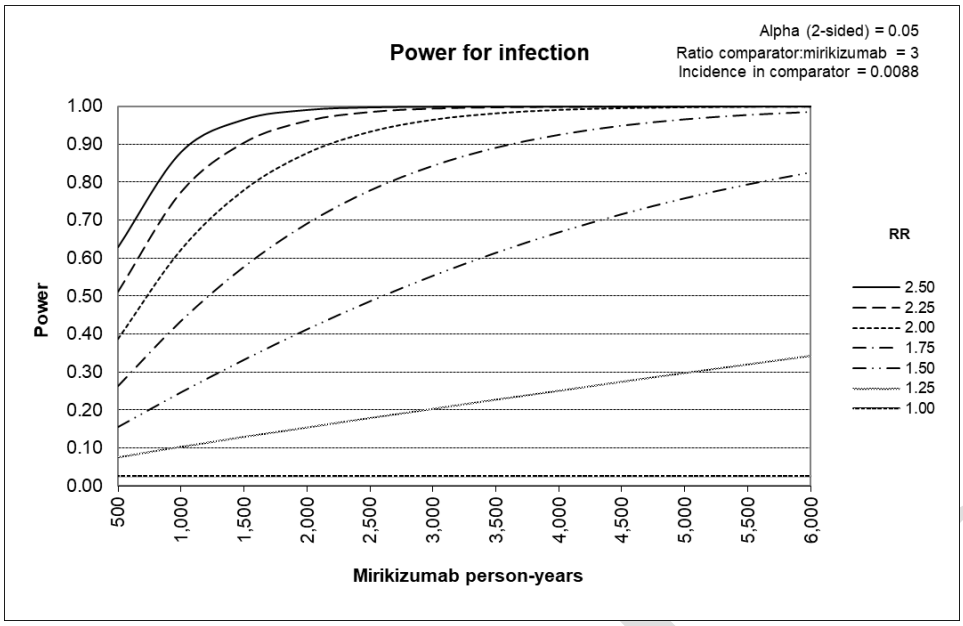
Figure 5. Power of the study to detect a range of relative risks for serious and opportunistic infections.



Abbreviation: RR = relative risk.

Table 5 illustrates the power to detect a RR of 2.0 for serious and opportunistic infections assuming a more conservative matching ratio of mirikizumab to comparators in each pairwise comparison (mirikizumab versus anti-TNF mABs, mirikizumab versus ustekinumab, mirikizumab versus vedolizumab, and mirikizumab versus S1P receptor modulators). Even under the most conservative matching ratio (1:1), the study will have more than 80% power to detect a minimum RR of at least 2.0 if at least 3000 person-years of mirikizumab are accrued.

Table 5. Power to Detect a Relative Risk of 2.0 for Serious and Opportunistic Infections[a] Under Alternate Assumptions

Mirikizumab:Comparator Ratio	Mirikizumab Person-years	Power to Detect RR of 2.0
1:1	3000	86.2%
	4000	94.3%
	5000	97.8%
	6000	91.9%
1:2	3000	94.5%
	4000	98.4%
	5000	99.5%
	6000	99.9%

Abbreviation: RR = relative risk.

[a] Assumes a 2-sided alpha level of 0.05 and an incidence rate of 880 per 100,000 person-years in the unexposed for serious and opportunistic infections.

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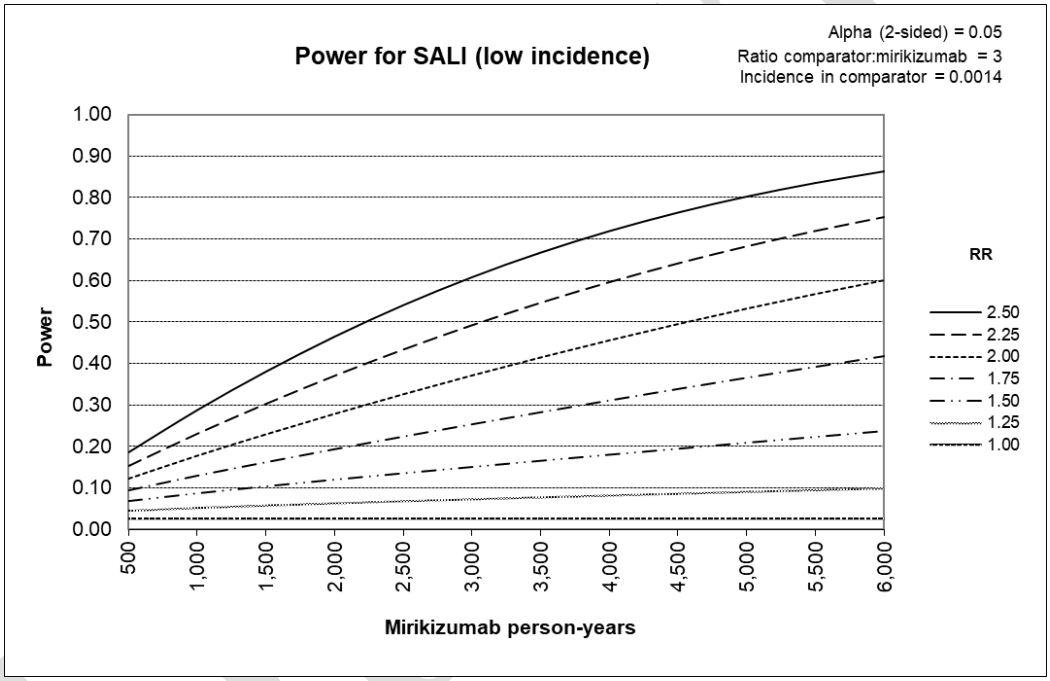
9.5.2.4. Severe Acute Liver Injury

SALI has a wide range of reported incidence rates between approximately 1.4 per 1000 person-years and 18.9 per 1000 person-years among anti-arrhythmic users within a claims data source (Gao et al. 2013). Assuming a matching ratio of 3 comparators per mirikizumab patient in each pairwise comparison (mirikizumab versus anti-TNF mABs, mirikizumab versus ustekinumab, mirikizumab versus vedolizumab, and mirikizumab versus S1P receptor modulators), the study will have approximately 80% power to identify a minimum RR of at least 2.5 if 5000 person-years are observed among mirikizumab initiators at the lower end of this incidence range and more than 90% power for a minimum RR of at least 1.5 if 5000 person-years are observed at the higher end of this range (Figure 6 and Figure 7).

Figure 6. Power of the study to detect a range of relative risks for SALI (low incidence).



Abbreviations: RR = relative risk; SALI = serious acute liver injury.

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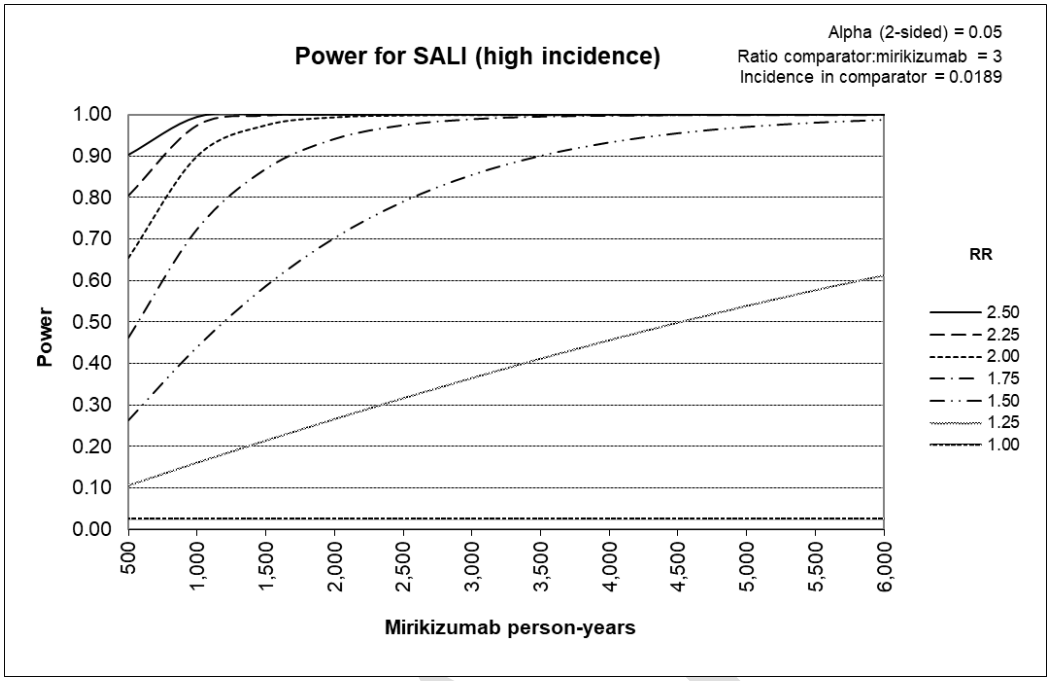
Figure 7. Power of the study to detect a range of relative risks for SALI (high incidence).



Abbreviations: RR = relative risk; SALI = serious acute liver injury.

Table 6 illustrates the power to detect a minimum RR of at least 2.5 for SALI assuming the true incidence is low (1.4 per 1000 person-years in the unexposed), as well as to detect a minimum RR of at least 1.5 assuming the true incidence is high (18.9 per 1000 person-years in the unexposed), under more conservative matching ratios of mirikizumab users to comparators (that is, 1:1 or 1:2) in each pairwise comparison (mirikizumab versus anti-TNF mABs, mirikizumab versus ustekinumab, mirikizumab versus vedolizumab, and mirikizumab versus S1P receptor modulators). If the incidence of SALI is low and the matching ratio is 1:1, the study will have low power to detect even a minimum RR of at least 2.5. However, if the incidence of SALI is high, the study will have approximately 80% power to detect a minimum RR of at least 1.5, even under the most conservative matching ratio of 1:1, as long as 4000 mirikizumab person-years are accrued.

Table 6. Power to Detect a Relative Risk of 2.5 Assuming Low-incidence[a] SALI and a Relative Risk of 1.5 Assuming High-incidence[b] SALI Under Alternate Assumptions

Mirikizumab:Comparator Ratio	Mirikizumab Person-years	Power to Detect RR of 2.5 Assuming Low Incidence	Power to Detect RR of 1.5 Assuming High Incidence
1:1	3000	36.4%	67.7%
	4000	47.3%	79.9%
	5000	57.2%	88.0%
	6000	65.7%	93.0%

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Mirikizumab:Comparator Ratio	Mirikizumab Person-years	Power to Detect RR of 2.5 Assuming Low Incidence	Power to Detect RR of 1.5 Assuming High Incidence
1:2	3000	53.5%	80.9%
	4000	65.1%	90.3%
	5000	74.3%	95.3%
	6000	81.4%	97.8%

Abbreviations: RR = relative risk; SALI = severe acute liver injury.

[a] 1.4 per 1000 person-years in the unexposed.

[b] 18.9 per 1000 person-years in the unexposed.

9.6. Data Management

This research study will only use data that will have already been collected for administrative insurance claims purposes at the time the analysis will be performed (that is, secondary data analysis). The ORD data are derived from claims submitted by providers and pharmacies to obtain payment for health care services rendered, data to track plan membership for premium billing, and provider data to track participating physicians who have contracts with health plans to provide services. The underlying administrative data are routinely captured, verified, automated, and de-identified. The data undergo regular audits and quality control procedures by the insurer and are updated monthly.

Study datasets and analytic programs will be kept on a secure server and archived per Optum's record-retention procedures. All analytic study data will be archived in accordance with Optum SOPs, unless specific requests are made during the report process, or unless study data sources have alternative archive requirements.

All analyses will be performed using SAS® version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and SAS Enterprise Guide 6.1 or later.

9.7. Data Analysis

9.7.1. Propensity Score Matching of the Comparison Cohorts to the Mirikizumab Cohort

Prior to all analyses, 4 conditional logistic regression models will be used to calculate the time-conditional propensity of receiving mirikizumab versus receiving (1) an anti-TNF mAB, (2) ustekinumab, (3) vedolizumab, or (4) a S1P receptor modulator within each dispensing-based exposure set as a function of the time-varying patient characteristics evaluated at the time of the exposure set (Figure 2) (Suissa et al. 2017). Each mirikizumab patient will then be matched to the 3 most similar (in terms of PS values) comparator patients in their exposure set, creating 4 matched cohorts in total: a cohort of mirikizumab patients matched to patients receiving anti-TNF mABs; a cohort of mirikizumab patients matched to those receiving ustekinumab; a cohort of mirikizumab patients matched to those receiving vedolizumab; and a cohort of mirikizumab

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patients matched to those receiving S1P receptor modulators. A greedy digit-based matching algorithm will be used, in which mirikizumab patients are matched without replacement to comparator patients at a given level of precision defined by the number of digits of the PS (Parsons 2001). When no further matches are available at a given level of precision, the number of digits is sequentially reduced until a maximum allowable calliper of 0.1 is reached, thereby ensuring that the matched cohorts are comparable with respect to the underlying measured risk factors.

In addition to adjusting for dispensing-based exposure sets, the conditional logistic regression models will also adjust for patient characteristics identified *a priori* as potential risk factors for the study outcomes (that is, the covariates in Section 9.3.5). As there are 4 study outcomes, each with its own set of potential risk factors (Section 9.3.5) and outcome-specific exclusion criteria (Section 9.2.4.2), the propensity of receiving mirikizumab versus each of the 4 comparator treatments will be calculated as a function of the specific risk factors of each outcome, among only those patients who qualify for inclusion (that is, patients remaining after the application of the outcome-specific exclusion criteria). This will result in 16 core PS models and produce 16 matched cohorts. Because index dates are based on exposure sets defined by dispensing number, such that a mirikizumab user with an index date in 2024 may be matched with a comparator whose index date falls in a different year, the PS models will incorporate calendar year to accommodate changes in the way that UC drugs are used over time and adjust for calendar time.

The matched cohorts will be used to conduct all primary, secondary, and sensitivity analyses for the study outcomes. The 16 core PS models will be rerun within subgroups of interest (that is, patients aged 65 years of age or older), as these subgroups may have a different distribution of covariates from the overall patient population. Within each matched cohort, the distribution of risk factors between mirikizumab patients and comparator patients is expected to be balanced. Balance will be evaluated by overlaying graphs of the PS distributions in mirikizumab-exposed and comparator cohorts before and after matching to assess the extent of overlap between the mirikizumab initiators and comparators with respect to the PS (Suissa et al. 2017). Additionally, the standardized differences between the matched cohorts for each covariate in the model will also be assessed. Variables with an absolute standardized difference less than 0.1 will be considered balanced (Austin 2009). If a variable has an absolute standardized difference that is greater than 0.1 but less than 0.2, modifications to the appropriate PS models will be considered, depending on the importance of the risk factor. An absolute standardized difference greater than 0.2 will be defined as imbalanced. If imbalanced covariates are observed, further PS model modifications (for example, addition of interaction terms) or inclusion of the imbalanced covariates in the outcome models will be considered (Normand et al. 2001).

In addition to PS-matching, IPTW will be performed as a sensitivity analysis (Section 9.7.3.3).

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9.7.2. Descriptive Analyses

During the course of the study, Optum will produce progress reports for inclusion in Eli Lilly and Company's periodic updates to the regulatory agencies. Each progress report will include descriptive data on patients and follow-up accrued through the data cutoff period for that report. In particular, each report will enumerate new and prevalent users of mirikizumab during the corresponding accrual period; report on the duration of continuous enrolment since initiation of mirikizumab, and total duration of use; and describe the basic demographic characteristics (for example, age, sex, calendar year, geographic region in the US) of the mirikizumab cohort. Descriptive statistics will include the mean, median, standard deviation, and interquartile range for continuous variables, and absolute and relative frequencies for categorical variables. Progress reports will not include counts or descriptions of comparator medication patients.

In addition to the progress reports, Optum will produce 1 interim report based upon claims data on patients through the latest available data at the time of data extraction anticipated to occur in May 2030. All descriptive analyses will be based on the source populations remaining after application of all general and outcome-specific exclusion criteria. An attrition table and description of the study cohorts (including relevant baseline characteristics, such as demographics, medical and prescription drug history, and health care services) will be provided in this report. In addition, the duration of continuous enrolment since initiation of mirikizumab or comparator medication, and total duration of use of the medication of interest, will be described. The interim report will also include K-M survival curves for all outcomes. For each outcome of interest, crude incidence rates will be calculated within each treatment cohort, along with 95% CIs. K-M curves and crude incidence rates will also be presented for a subset of elderly patients aged 65 or older, sample size permitting.

9.7.3. Comparative Analyses

In the interim and final reports, comparative analyses (primary, secondary, and sensitivity) will be presented only for those study outcomes for which there is sufficient sample size accrued to detect a minimum RR of at least 1.5 to 2.5, depending on the outcome, at 80% power (Section 9.5.2). For example, if, at the interim and final analyses, there are 3000 person-years accrued in the mirikizumab cohort and each mirikizumab patient is successfully matched to 3 comparators, the analysis will likely have sufficient power to detect a minimum RR of at least 2.0 for MACE, malignancies, and infection; therefore, comparative analyses at the interim and final analysis will be restricted to these outcomes only.

Additionally, the final report will present the results of the medical record adjudication process for SALI (for example, number of medical records sought, the number retrieved, and the PPV) and the results of the NDI search for CV deaths. The final report will also contain a second set of comparative analyses, limiting SALI and CV death to confirmed outcomes, as sample size allows.

As mirikizumab patients will be PS-matched to comparator patients, Cox PH models utilizing robust variance estimators that account for clustering within matched sets (Austin 2014) will be used in all primary, secondary, and sensitivity analyses to allow for accurate estimation of the

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sampling variance of the estimated log-hazard ratio. The HRs and corresponding 95% CI of each study outcome will be estimated among mirikizumab users compared to PS-matched users of: (1) anti-TNF mABs, (2) vedolizumab, (3) ustekinumab, and (4) S1P receptor modulators, separately. For all Cox models, appropriate diagnostic tests will be conducted on the modelling assumptions, including a test for PH. If hazards are found to be non-proportional, an alternative approach will be to use a piecewise hazards model to divide follow-up time into segments that meet the PH assumption (Gregson et al. 2019).

9.7.3.1. Primary Analysis

In the primary analysis for the long-latency outcome of malignancy, follow-up will begin 1 year from the day following the index date (as described in Section 9.2.7). This analysis will not account for change in exposure during follow-up, but rather patients will be followed as though they had not switched from their first index therapy.

In the primary analysis for the shorter latency outcomes of MACE, serious and opportunistic infections, and SALI, patients who switch from a comparator to mirikizumab will be followed in the comparator cohort up to the point of the switch, and in the mirikizumab cohort afterwards (Section 9.2.7). To account for the potential impact of this non-independence in the estimation of CIs, bootstrap sampling will be conducted as a sensitivity analysis. In contrast, patients who start in the mirikizumab cohort and later switch to a comparator medication will be included in the mirikizumab group for the duration of mirikizumab use and any follow-up time until the initiation of the comparator, at which point their follow-up will be censored. In accordance with the study objective (Section 8), the primary analysis will also be conducted among the subset of patients aged 65 years or older as sample size allows.

9.7.3.2. Secondary Analyses

For the malignancy outcome, a secondary analysis will be performed that will account for switching of medications during follow-up, like in the primary analysis for the shorter latency outcome. Patients who switch from a comparator to mirikizumab will be followed in the comparator cohort up to the point of the switch, and the mirikizumab cohort afterwards; as described in Section 9.7.3.1, bootstrap sampling will be conducted as a sensitivity analysis to account for the potential impact of non-independence in the estimation of confidence intervals. Mirikizumab patients who later switch to a comparator treatment will be censored at the time of the switch. Moreover, in this secondary analysis for malignancy, follow-up will begin on the day following the index date, rather than 1 year later as was the case in the primary analysis (Section 9.2.7).

For the MACE outcome, a secondary analysis will include stratification by previous history of MACE as an alternative to excluding patients with prior MACE diagnoses.

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9.7.3.3. Sensitivity Analyses

A sensitivity analysis will be conducted in which the primary analysis is repeated after restricting the study population to patients with a minimum of 12 months of continuous enrolment prior to and including the index date. This sensitivity analysis will continue to use all available data prior to and including the index date to evaluate history of UC treatment and other key covariates (Section 9.2.6 and Section 9.3.5).

In another sensitivity analysis, the primary analysis for MACE will be restricted to the subset of patients in the study population that can be linked with the NDI death data.

For the outcome of malignancy, the duration of exposure to mirikizumab (for the mirikizumab patients), and anti-TNF mABs or biosimilar, ustekinumab or biosimilar, vedolizumab, or S1P receptor modulators (for the respective comparator patients) will be estimated based on per-label dosing schedules. The main analysis will then be repeated with duration of treatment included as an added covariate in each model.

Additionally, another sensitivity analysis will be conducted in which the primary analysis is repeated using IPTW instead of PS-matching.

Lastly, a quantitative bias analysis will evaluate the impact of potential unmeasured or uncontrolled confounding in accordance with the Schneeweiss method, which estimates the magnitude of confounding that would be necessary to fully explain the observed risk ratio (Schneeweiss 2006; Liang et al. 2019).

The current study timeline specifies that the final version of the report will be submitted on 31 December 2037. However, if the progress reports for this study indicate that sufficient study size will be reached prior to the planned end of accrual, the end of accrual and follow-up for the final reports may be advanced to allow Optum to provide the final report earlier.

9.7.4. Missing Data

This study is based on an analysis of automated medical and prescription claims data, supplemented by information abstracted from medical records. Using the standard approach in claims data analyses, the presence of a medication or disease claim will be assumed to indicate use of that medication or the presence of that disease and conversely, the absence of a medication or disease claim will indicate the absence of use of that medication or a diagnosis of that disease.

In general, missing data will not be imputed, and data will be analysed as they are recorded with the exception that in developing the PS model, missing data for clinically important variables (for example, BMI) may be imputed using multiple imputation. If any variables are imputed, the missing at random assumption will be considered. The decision to use a missing indicator versus multiple imputation for missing values will be made on a variable-by-variable basis, considering the proportion of patients with missing values. Hence, all patients will have a calculated PS and no patients will be excluded from the analysis due to missing data.

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9.8. Quality Control

This research study will use ORD and MA-PD data derived from claims submitted for payment. Although the health insurance claims data represent financial transactions and are not research records, the financial transactions related to the services provided create financial incentives to record them correctly and fully, so the billable medical services represented in the database are likely to be complete. The validity of this claims research database for epidemiologic research (as compared to data abstracted from medical records) has been widely published (Quam et al. 1993; Dore et al. 2011; Laughlin 2011; Eng et al. 2012).

The study will be carried out according to Optum Epidemiology's internal SOPs that are consistent with the Guidelines for Good Pharmacoepidemiology Practices published by the EMA and International Society for Pharmacoepidemiology (EMA 2017; PPC-ISP 2016), as well as the FDA's Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data (FDA 2013).

Programming for this project will be conducted by a primary analyst and validated by a separate analyst (validation analyst). Validation of all statistical programs and results consists of a combination of visual checks (that is, examination of the programming log, visual printouts before and after data management steps, and so on) and computational checks (that is, repeating calculations for comparison purposes) performed by a validation analyst. In addition, 2 epidemiologists and a senior scientist perform a substantive review of study tables, reports, and all other deliverables for plausibility and internal consistency. All validation and quality control procedures are conducted in accordance with Optum SOPs, which prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

9.9. Limitations of the Research Methods

This study is based on analysis of automated medical and prescription claims, supplemented by information from the medical record, mortality data from the SSA and public obituaries, and linkage to the NDI. While claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, health care resource utilization, and costs, all claims databases have certain inherent limitations because the claims are collected for the purpose of payment, not research. The presence of a diagnosis code on a medical claim is not confirmation of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. However, we strove to address this limitation by using validated claims algorithms for UC and study outcomes that rely on other elements in addition to a single diagnostic code. Additionally, a medical record review will be conducted to confirm SALI outcomes.

Another limitation of claims data relates to potential misclassification of exposure. The presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Medications filled over the counter or provided as samples by the physician will not be observed in the claims data. For instance, if samples of biologics are given to patients within the study population, we will not be able to detect or incorporate these into

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treatment episodes. Similarly, we may not have complete history of treatment for individuals who enter the ORD or MA-PD databases from a different insurer, having had previous experience with UC treatments. Misclassification of exposure has the potential to compromise the integrity of our study design, which requires accurate matching on treatment history. However, we have taken steps to address these limitations. In addition to matching on number of prior dispensings, our main analysis also matches on type of UC treatment (that is, anti-TNF mABs versus vedolizumab versus ustekinumab versus S1P receptor modulators; Section 9.2). To the extent that these factors represent later lines of therapy, matching on them is expected to produce study cohorts that are at the same point in their treatment journey at their index date. Similarly, medications dispensed but not consumed are unlikely to be an issue given they are indicated for treatment of moderately to severely active UC and the cost associated with biologic treatments.

Imperfect capture of over-the-counter medication use may also impact covariate assessment. For instance, acetaminophen, a commonly used over-the-counter medication, is a risk factor for liver injury at high doses. However, in our study, acetaminophen use can only be observed for pharmacy dispensings that resulted in a claim, potentially leading to an underestimate of total quantity used.

The study power will be limited until several years of cohort accrual and outcome identification have passed. Because accrual of mirikizumab patients depends on actual use within the insured population that is the source for the study, and mirikizumab was only recently approved in the US for the treatment of UC, it may be several years until study power reaches an adequate level. In the event that the accrual of mirikizumab patients is slower than expected, the extension of the accrual period and/or the addition of a data partner may be considered.

The planned comparative analyses also suffer from limitations. The primary analysis for the long-latency outcome of malignancy does not intend to account for change in exposure during follow-up, but rather will continue to follow patients as though they had not switched from their first index therapy as described in Section 9.2.7. By not censoring at the point of the switch, this approach has the advantage of preserving follow-up for as long as possible to better enable the identification of long-latency cancers. However, comparators who switch to mirikizumab but are treated as comparators will in fact be exposed to both their comparator medication and mirikizumab. This may bias effects towards the null if comparator treatment followed by mirikizumab produces an outcome effect similar to that of mirikizumab alone. To address this limitation, a secondary analysis has been planned for the malignancy outcome that censors comparators at the point of switching to mirikizumab (Section 9.7.3.2).

For the shorter latency outcomes of MACE, serious and opportunistic infections, and SALI, the planned primary analysis allows for patients who switch from a comparator to mirikizumab to be followed in the comparator cohort up to the point of the switch, and in the mirikizumab cohort afterwards (Section 9.2.7). By censoring at the point of the switch, this analysis keeps the effects of comparator medications separate from those of mirikizumab. However, it does so at the expense of limiting the available follow-up time and consequently, the power to detect an effect. Additionally, the potential impact of re-using comparators may be a limitation of prevalent user

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studies (Suissa et al. 2017); a sensitivity analysis will use bootstrap sampling to address this potential limitation.

Another limitation of observational studies is that treatment is not randomly assigned, and there is potential for unmeasured confounding by factors not captured in automated data. To address this concern, a quantitative bias analysis will be conducted, evaluating the degree of unmeasured confounding needed to account for the observed associations (Section 9.7.3.3). Residual confounding due to incomplete adjustment is another concern. For example, US product labels for adalimumab, golimumab, and infliximab contain warnings that these anti-TNF mABs increase the risk of serious infection, malignancies, and congestive heart failure, and the infliximab label additionally warns of an increased risk of cerebrovascular accidents, myocardial ischemia/infarction, hypotension, hypertension, arrhythmias and stroke (Humira package insert, 2021; Remicade package insert, 2021, Simponi package insert, 2018). The ustekinumab label warns of an increased risk of infections and malignancies, while the vedolizumab label warns of an increased risk of infections and liver injury (Stelara package insert, 2023; Entyvio package insert, 2022). Given these warnings, a type of confounding known as channelling bias may occur if physicians preferentially prescribe mirikizumab to patients with risk factors for these outcomes (Weinstein et al. 2020). To mitigate this bias, we will implement outcome-specific exclusion criteria (Section 9.2.4.2), such that, for instance, patients with the strongest risk factor for MACE – a prior history of MACE – are excluded from all cohorts in the MACE analysis. These patients would be prime candidates for channelling away from a particular class of treatments towards others and excluding them from all cohorts would remove this potential source of bias. As another mitigation strategy, we will empirically identify the most frequent baseline diagnoses, medications, and procedures in the mirikizumab versus the comparator cohorts (Section 9.3.5). If, for example, baseline cardiomyopathy is found to be more frequent in the mirikizumab cohort than in comparators, suggesting that patients with this condition are being preferentially treated with mirikizumab, we will incorporate cardiomyopathy into the PS model to reduce the potential for channelling bias in the MACE analysis.

Lastly, patients in the main analysis will be required to have a minimum of 6 months of baseline data for covariate assessment. This 6-month interval represents an effort to balance adequate time for covariate assessment with the need to conserve sample size. However, 6 months may not be sufficient to assess chronic medical conditions potentially relevant to the current study outcomes (that is, a previous cancer diagnosis). To address this limitation, we have incorporated a sensitivity analysis that requires a minimum of 12 months of baseline data prior to and including the index date (Section 9.7.3.3). Furthermore, in the main analysis, the assessment of select covariates (Section 9.3.5) will extend beyond the 6 months of minimum required baseline data to incorporate all available information from the secondary data up to 5 years prior to and including the index date.

9.10. Other Aspects

Not applicable.

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10. Protection of Human Subjects

Observational studies will be submitted to ERBs for approval whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with applicable laws and regulations of the region, country, or countries where the study is being conducted, as appropriate.

Confidentiality of patient records will always be maintained. All analyses will be performed in accordance with applicable laws and regulations. All reports will contain aggregated results only and will not identify individual patients, physicians, facility, claims, or record data. The final table shells/analytic output are subject to change pursuant to Optum's standard statistical de-identification review process. For this reason, Optum may require certain modifications to the output layout to manage the statistical risk of re-identification. At no time during the study will Eli Lilly and Company receive patient-identifying information.

10.1. IRB Approval

Optum will prepare and submit the appropriate documents to a central IRB for Optum's conduct of the project. Optum will communicate directly with the IRB to address any questions and/or provide any additional information in connection with the review. Approval from an IRB for this project is not guaranteed. This project will be undertaken only after the study protocols and study documents have been approved by the IRB and Optum is granted a waiver of authorisation. The IRB will monitor the study for the life of the project and may require formal re-review and approval on an annual basis. Changes to the project may also require re-review and approval by the IRB.

10.2. Application for Approval of Medical Record Abstraction

One application will be submitted to an IRB for approval of the medical record abstraction process and documents. The application will likely include the following documents:

- Study protocol and
- Medical record procurement/abstraction form.

Optum internal review and approval processes are also required. Optum will provide general study information and a copy of the IRB approvals and waiver documents to internal reviewers for approval to use such data source's data in the study, which is not guaranteed.

10.3. Application for Approval of Data Linking

Accessing certain data fields necessary to link data sources requires IRB approval. Following receipt of the necessary approval and a waiver of authorisation from an IRB, which are not guaranteed, Optum can apply to the relevant data sources to link the subjects included in the study to the NDI death data (for CV death). Optum will provide a copy of the IRB approval and waiver documents and general study information as part of that application. Approval for linking

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to NDI data is not guaranteed. Approved NDI users agree that no data will be published or released in any form, including for purposes of adverse event reporting to any party, if a particular individual or establishment is identifiable.

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11. Management and Reporting of Adverse Events/Adverse Reactions

This research study will use only data that have already been collected at the time the research is performed (that is, secondary data analysis). Based on current guidelines from International Society for Pharmacoepidemiology and the European Medicines Agency (EMA 2017; PPC-ISP 2016), non-interventional studies such as the one described in this study protocol, conducted using medical chart reviews or electronic claims and health care records, do not require reporting of adverse events or reactions.

11.1. Secondary Data Use Study

This is a non-interventional study based on secondary data use, and therefore, no Individual Case Safety Report (ICSR) reporting is required. The study protocol-defined AEs include MACE, malignancies excluding NMSC, serious and opportunistic infections, and SALI (Section 9.3.4). All protocol-defined adverse events collected will be summarized in the interim and final study report. No other AEs will be collected.

11.2. Product Complaints

The collection and reporting of product complaints is not applicable to the current study, which is based on health insurance claims data. Product complaints are not collected for medications or medical devices that appear in health insurance claims.

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12. Plans for Disseminating and Communicating Study Results

Study progress reports will be submitted with the PSUR. An interim and final study report will be submitted to regulatory agencies. The study, including the final report, will also be registered in the ENCePP Registry. The study findings may be submitted to a scientific congress and/or to a peer-reviewed journal.

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Annex 1. List of Standalone Documents

No.	Document Reference No.	Date	Title
1	TBD	TBD	Study outcomes and covariates code lists

Abbreviations: No. = number; TBD = to be determined.

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Annex 2. ENCePP Checklist for Study Protocols

Study title:
Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data

EU PAS Register® number: EUPAS105671
Study reference number (if applicable): I6T-MC-B004

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[3] Date from which the analytical dataset is completely available.

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Section 2: Research question	Yes	No	N/A	Section Number
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is an observational study that does not rely on the hypothesis testing paradigm. Rather, the goal is to quantify the magnitude and precision of an effect estimate that assesses occurrence of adverse events, so as to provide additional information for regulatory decision-making.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4, 9.6, 11.1
3.3 Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2

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Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.2 Age and sex	☒	☐	☐	9.2
4.2.3 Country of origin	☒	☐	☐	9.4
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.7
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3, 9.7.3.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.2.7, 9.3.2, 9.3.3
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2

Comments:

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Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.4
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.4
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.4, 9.3.4.5
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2.2.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7, 9.9

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

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Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3, 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3, 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	

Comments:

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Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytical control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytical control of outcome misclassification?	☒	☐	☐	9.7, 9.9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

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Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

DRAFT

Approved on 18 Apr 2024 GMT

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____PPD_____

Date: 03-April-2024

Signature: _____PPD_____

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Approved on 18 Apr 2024 GMT