Protocol I1F-MC-RHBT(b)
A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (may include psoriatic arthritis) in the Course of Routine Clinical Care

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PASS Information

Title	**I1F-MC-RHBT**: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (may include psoriatic arthritis) in the Course of Routine Clinical Care
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Joint PASS	No
Research question and objectives	The primary objective of the study is to examine the incidence of malignancy, excluding non-melanoma skin cancer (NMSC), among patients with psoriasis exposed to ixekizumab in routine clinical practice relative to nonbiologic systemic medications (NBSM) and non-IL-17 biologic medications used to treat psoriasis. The secondary objective is to examine the incidence of NMSC, serious infections, opportunistic infections (including active tuberculosis), inflammatory bowel disease (IBD), major adverse cardiovascular events (MACE), serious hypersensitivity reactions, demyelinating disease, and gastrointestinal perforation among patients with psoriasis exposed to ixekizumab in routine clinical practice relative to NBSM and non-IL-17 biologic medications used to treat psoriasis. A further objective is to obtain information about the safety of ixekizumab in the very elderly (≥75 years of age).
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Marketing Authorization Holder

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1. Table of Contents

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2. List of Abbreviations

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
Baseline	Entry into a treatment cohort is considered baseline and can occur at enrolment (incident or prevalent user) or upon initiation of a non-IL-17A biologic or ixekizumab during follow-up
BSA	body surface area
CI	confidence interval
CRF	case report form
DALY	disability-adjusted life year
DMARD	disease-modifying anti-rheumatic drug
Drug Initiation	A drug initiation is the first use of the specific drug by a patient.
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS	European Union post-authorisation safety
FDA	Food and Drug Administration
GC	glucocorticoid
GEE	generalized estimating equation
HR	hazard ratio
HRQoL	health-related quality of life
IBD	inflammatory bowel disease (includes Crohn's disease and ulcerative colitis)

Term	Definition
IL	interleukin
Index Date	The index date is the start of a drug exposure period for the current study and is the date of a treatment start for a medication started at or after enrolment and the date of registry enrolment for a medication initiated prior to registry enrolment.
Incident User	An incident user is a patient that initiates a new drug at the time of registry enrolment or initiates a new drug after registry enrolment.
IRB	institutional review board
MACE	major adverse cardiac events
MI	myocardial infarction
NBSM	nonbiologic systemic medication(s)
NMSC	non-melanoma skin cancer
NPF	National Psoriasis Foundation
PASS	post-authorization safety study
Prevalent User	A prevalent user is a patient with ≤ 12 months of drug exposure at the time of registry enrolment.
QALY	quality-adjusted life year
RA	rheumatoid arthritis
Restarter	A restarter is a patient who is re-using a drug that that was previously used.
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
Switcher	A switcher is a patient already enrolled in the study who switches to a new drug. Multiple switches can be observed.
TAE	targeted adverse event
TNF-α	tumour necrosis factor alpha
US	United States

Term	Definition
WHO	World Health Organization

3. Responsible Parties

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4. Abstract

A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (may include psoriatic arthritis) in the Course of Routine Clinical Care

Version: 3.0; approval date can be found at the bottom of Page 1

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Rationale and Background

In addition to the safety data offered by registration trials, dermatologists, regulators, and patients with psoriasis have an interest in better understanding the long-term safety of biologics and other new therapies entering the market. Ixekizumab is an interleukin (IL)-17A antagonist approved for the treatment of moderate-to-severe plaque psoriasis and active psoriatic arthritis. Data from clinical trials demonstrate that ixekizumab is effective and generally well tolerated; however, the long-term safety profile among patients treated in routine clinical practice is not fully characterized. The purpose of this study is to assess the long-term safety of ixekizumab compared with other systemic therapies used in the treatment of adults with moderate-to-severe psoriasis (may include psoriatic arthritis) in the course of routine clinical care. The study is being completed to address Eli Lilly and Company's (Lilly's) post-authorization regulatory requirements.

The Corrona Psoriasis Registry Protocol is supported by multiple pharmaceutical companies and is an operational protocol. As a result, it is not designed to address analytic objectives associated with a specific product. This document outlines Lilly's specific objectives, study design, and planned analyses of Corrona Psoriasis Registry data related to ixekizumab. It is intended to serve as Lilly's analytic protocol, to be conducted within the registry population and under the governance of the Corrona Psoriasis Registry Protocol. The Corrona Psoriasis Registry is sponsored and operationalized by Corrona. Lilly is providing funding support for the Corrona Psoriasis Registry, analyses specified under this analytic protocol, and associated safety surveillance activities.

Research Question and Objectives

The primary objective of the study is to examine the incidence of malignancy, excluding non-melanoma skin cancer (NMSC), among patients with psoriasis exposed to ixekizumab in routine clinical practice relative to nonbiologic systemic medications (NBSM) and non-IL-17 biologic medications used to treat psoriasis.

The secondary objective is to examine the incidence of NMSC (Section 9.3.2.2), serious infections (Section 9.3.2.3), opportunistic infections [including active tuberculosis (Section 9.3.2.4)], inflammatory bowel disease [IBD (Section 9.3.2.5)], major adverse cerebro-cardiovascular events [MACE (Section 9.3.2.6)], serious hypersensitivity reactions (Section

9.3.2.7), demyelinating disease (Section 9.3.2.8), and gastrointestinal perforation (Section 9.7.7.8) among patients with psoriasis exposed to ixekizumab in routine clinical practice relative to NBSM and non-IL-17 biologic medications used to treat psoriasis. A further exploratory objective is to obtain information about the safety of ixekizumab in the very elderly (≥75 years of age).

Study Design

This study uses a cohort design to assess prospectively collected data from the Corrona Psoriasis Registry, an existing, prospective, multicentre, observational psoriasis registry. All protocols for comparative research are subject to Corrona approval and will be executed by Corrona statisticians.

Study Population

The study population includes all patients in the Corrona Psoriasis Registry, with some exclusions employed for specific analyses. Patients in the Corrona Psoriasis Registry must be at least 18 years of age, have psoriasis (which may include patients who also have comorbid psoriatic arthritis) diagnosed by a dermatologist, and have initiated a United States (US) Food and Drug Administration (FDA)-approved systemic psoriasis treatment within the previous 12 months (includes FDA-approved biologic treatments for psoriasis and methotrexate, cyclosporine, or apremilast). Patients who are unable or unwilling to provide informed consent to participate in the registry, who are enrolled in a clinical trial, or who are restarting the same systemic medication <12 months from the previous stop at the time of enrolment are excluded. Patients with exposure to drugs in the same class as ixekizumab (IL-17 inhibitors) will also be excluded as described below.

Variables

During the course of routinely scheduled clinic visits, data on a select number of clinical characteristics relating to psoriasis activity and disease severity, comorbidities, concomitant medications, and targeted adverse events (TAEs) will be collected directly from patients and through providers by means of study forms. Results of diagnostic testing will also be recorded based upon the availability of results from routine clinical care.

The primary outcome of this study is malignancy, excluding NMSC. Secondary outcomes include NMSC, serious infections, opportunistic infections (including active tuberculosis), IBD, MACE, serious hypersensitivity reactions, demyelinating disease, and gastrointestinal perforation.

Potential confounding variables include demographics, medical history and comorbidities, health behaviours, psoriasis disease duration, psoriasis severity, and treatment.

Exposure Classification

Drugs used to treat patients with psoriasis will be considered in 3 exposure groups or cohorts: NBSM cohort, non-IL-17 biologics cohort, and the ixekizumab cohort. Follow-up time will begin at index date (treatment start for medication started at or after enrolment; enrolment date

for medication initiated prior to registry enrolment) and continue until an incident event, start of another medication, end of study period, withdrawal from the registry, or death.

Drug exposures will be classified differently for the evaluation of malignancy excluding NMSC, and NMSC, to accommodate the prolonged temporal relation expected between the diagnosis of a cancer and any putative causal exposure. Specifically, assignment to exposure groups will be hierarchical: once exposure to a biologic medication occurs, subsequent person-time may not be attributed to the NBSM cohort. Similarly, once exposure to ixekizumab occurs, time may not be attributed to other cohorts. Alternative cohort definitions will be examined as sensitivity analyses.

For outcomes other than malignancy, an 'as-treated' approach, in which person-time will accrue based on the treatment received, without regard to a hierarchy, will be used. Follow-up time will begin at treatment start and continue until an incident event, start of another medication, end of study period, withdrawal from the registry, or death. When a patient switches medication, even within an exposure group, a new index date will be assigned. New and continuing user status will be updated at each time point.

Drugs in the same pharmacological class as ixekizumab will be excluded from all exposure cohorts to allow for investigation of potential class effects, should any exist.

Before analyses occur, drug exposure patterns will be examined to ensure that predefined exposure cohorts properly represent exposure in the general population. Changes to the exposure cohorts may be made to reflect real-world use.

Data Source

Data for this study come from the Corrona Psoriasis Registry, launched in April 2015, in collaboration with the National Psoriasis Foundation (NPF). This registry mirrors the established Corrona Rheumatoid Arthritis (RA) Registry and will be cooperatively managed by scientific, operational, and quality leaders at Corrona and medical leaders appointed by the NPF. The objectives of this registry are to study the safety and effectiveness of biologic medications used to treat psoriasis.

Study Size

The registry anticipates capturing 4000 ixekizumab exposed patients and a minimum of 4000 non-IL-17 comparator patients. Follow-up for each patient will be for a minimum of 8 years. The current protocol will utilize the Corrona database to address study objectives. The final study size for this protocol will depend on the number of patients available within the Corrona Psoriasis Registry.

Control for Confounding

Calendar specific propensity score estimation, trimming for common support, and matching will be used to control for confounding. The propensity score model will be finalized before initiating any safety outcomes analyses. The primary approach will be the trimmed (for common support) population with a sensitivity analysis using the matched population.

Data Analysis

For all analyses, ixekizumab will be the treatment of interest. Comparisons will be made with the non-IL-17-biologic cohort and the NBSM cohort with the primary comparison between ixekizumab and non-IL-17 biologic cohort, where appropriate.

The number of NBSM users is expected to be small. Comparisons with this group of patients is intended to provide information about the potential risk of secondary outcomes associated with ixekizumab that may not be found with a comparison to other biologic medication. Differences that may be present between patients treated with NBSMs and those treated with ixekizumab may not be addressed by propensity scores (for example, differences in disease progression) and those differences may be important for determining the incidence of the outcomes of interest; therefore, these analyses will be exploratory.

Analyses of Malignancy (excluding NMSC) and NMSC

Baseline demographic and clinical characteristics for each exposure cohort will be examined, as well as the crude rate, per 100 patient-years, for all malignancies (excluding NMSC), NMSC, and malignancies by type. Cox proportional hazards regression will be used to estimate the risk in ixekizumab vs. comparator group by estimating the HR and associated two-sided 95% confidence interval in the propensity score trimmed populations. Any covariates chosen a priori or not balanced in the trimmed populations will be included in the Cox model. Proportional hazard assumptions will be tested and time varying covariates will be used. Sensitivity analysis will include completing the Cox model analysis with matched populations. Additionally, sensitivity analyses that examine the effect of unmeasured confounding, the association between the duration of ixekizumab exposure and the risk of malignancy, the effect of 6 and 12-month latency windows, and the possibility of detection bias are planned. The rate of malignancies will also be evaluated in very elderly patients (≥75 years of age).

Secondary Analyses (excluding NMSC)

Exposure time will be classified as ixekizumab, NBSM, or non-ixekizumab biologic medication use, based on the patient's time on each individual drug. For biologic medication exposures, a 90-day risk window will be constructed such that an event occurring within 90 days of drug discontinuation will be attributed to that exposure, unless the patient starts a new medication within the 90-day window.

Baseline characteristics for each exposure cohort will be examined, and the crude rate, per 100 patient-years, will be calculated for each cohort. Initial comparability between the exposure groups will be examined by standardized differences. Propensity score methods (such as trimming for common support and matching) will be used.

Cox proportional hazards regression will be used to estimate the risk in ixekizumab vs comparator cohorts by estimating the hazard ratio (HR) and associated two-sided 95% confidence interval in the propensity score trimmed populations. Any covariates chosen a priori or not balanced in the trimmed populations will be included in the Cox model. Censoring is defined as end of the study period, 90 days following discontinuation of a medication,

withdrawal from the registry, incident event, or death. Proportional hazard assumptions will be tested and time varying covariates will be used. Sensitivity analysis will include completing the Cox model analysis with matched populations. Additionally, several sensitivity analyses are planned including using a 30-day window following discontinuation. The rates for these outcomes will also be evaluated in very elderly patients (≥75 years of age).

Milestones

Data collection for the ixekizumab cohort began 20 April 2016. An interim report will be completed when 4000 ixekizumab patients have accrued. The final study report will be submitted by 31 May 2030.

5. Amendments and Updates

Amendment	Date	Section of Study Protocol	Amendment or Update	Reason
1	31 May 2019	2	Updated abbreviation table	
1	31 May 2019	3	Updated Responsible Party	Updated to reflect current team
1	31 May 2019	4	Updated abstract with clarifying text	Updated for clarity
1	31 May 2019		Added milestones to the abstract	Added upon realization that these were not included in the initial protocol per Lilly's template, which is based on GVP Module VIII
1	31 May 2019	6	Updated rationale and background with clarifying text	Updated for clarity
1	31 May 2019	7	Updated research question and objective with clarifying text	Updated for clarity
1	31 May 2019	9.3.1	Updated drug exposure with clarifying text	Updated for clarity
1	31 May 2019	9.3.1	Updated Tables 1 and 2	Updated for reflect additional approved therapies
1	31 May 2019	9.3.1.3.2	Updated Figure 1	Updated for clarity
1	31 May 2019	9.3.2	Updated Outcome and added both definite and probable for main analysis	Updated for clarity on adjudication process and outcome definitions
1	31 May 2019	9.3.2.5	Updated information regarding the inflammatory bowel disease TAE form	Updated to reflect the addition of the TAE form to the registry
1	31 May 2019	9.7	Updated Data Analysis with clarifying text	Updated for clarity on the interim report
1	31 May 2019	9.7.1	Updated Analysis Population with clarifying text	Updated for clarity
1	31 May 2019	9.7.3	Updated Propensity Score Definition and Estimation to include accounting for temporal variability	Updated for clarity
1	31 May 2019	9.7.4	Propensity score trimming for common support will be the primary approach and propensity score matching will be used as a sensitivity analysis	Updated for clarity and sample size considerations
1	31 May 2019	9.7.5	Clarifying text added	Updated for clarity
1	31 May 2019	9.7.6	Clarifying text added	Updated for clarity
1	31 May 2019	9.7.7	Clarifying text added	Updated for clarity
1	31 May 2019	9.7.8	Clarifying text added	Updated for clarity

Amendment	Date	Section of Study Protocol	Amendment or Update	Reason
1	31 May 2019	9.7.8.3	Sensitivity analysis for 30-day window added	Updated based on feedback
1	31 May 2019	9.9.1	Clarifying text added	Updated for clarity
2	07 Oct 2019	9.2.4	Added Canada to the list of study sites	Corrona now includes Canadian sites.
2	07 Oct 2019	9.3.1	Added newly approved medications to Tables 1 and 2	New medications were approved since this protocol was last approved.
2	07 Oct 2019	9.3.3	Removed glucocorticoids, corticosteroids, beta blockers, ACE inhibitors, penicillin, and cephalosporin from Table 3.	Capture of *all* concurrent medications not used for the treatment of psoriasis is not performed in the registry. The table was updated to remove medications that are not systematically collected and not able to be used as covariates.
2	07 Oct 2019	9.3.3	Changed dyslipidemia to hyperlipidemia	Changed to reflect option on data collection forms
2	07 Oct 2019	9.3.3	Added timing of personal history of malignancy with respect to the index date	Improves control of confounding when used in propensity score models
2	07 Oct 2019	9.7.6	Added presentation of the crude rate of malignancy by exposure time	The additional analysis will evaluate potential increases in event rates associated with increasing exposure.
2	07 Oct 2019	9.7.6	Added wording to clarify that history of malignancy at baseline will be examined by exposure cohort	Updated for clarity
2	07 Oct 2019	9.7.6, 9.7.7.1	Removed requirement that patients with an active malignancy at baseline be removed from analyses, and removed analyses that described patients with active malignancy at baseline	Changed due to limitations in the data to identify patients with active malignancy. Additional control for history of malignancy was added.
2	07 Oct 2019	9.7.7	Added presentation of the crude rate of secondary outcomes by exposure time	The additional analysis will evaluate potential increases in event rates associated with increasing exposure.

Amendment	Date	Section of Study Protocol	Amendment or Update	Reason
2	07 Oct 2019	9.7.7, 9.7.7.2 9.7.7.3	Removed requirement that patients with a prevalent secondary outcome be excluded from analyses, and removed analyses that described these excluded patients	Changed due to limitations in the data to identify patients with active acute events. History of the outcome will be described.
2	07 Oct 2019	9.7.7.2, 9.7.7.8	Removed glucocorticoid use from models	Glucocorticoid use is not systematically collected and cannot be included as a covariate.
2	07 Oct 2019	9.7.8.1.8	Changed section heading and rewrote section for clarity	Updated for clarity
2	07 Oct 2019	9.7.8.1.9	Changed section heading and rewrote section for clarity	Updated for clarity
2	07 Oct 2019	9.9.6	Added a section on the limitations associated with the capture of concurrent, non-psoriasis medications	Updated to reflect limitations of data capture in the registry

6. Milestones

Milestone	Planned Date
Start of data collection	20 April 2016[a]
End of data collection	30 September 2028
Interim report	To be initiated once the registry accrues 4000 ixekizumab exposures
Registration in the EU PAS Register	24 October 2018
Final report of study results	31 May 2030

[a] The study is being conducted within an independent registry, the Corrona Psoriasis Registry. Corrona enrolled the first ixekizumab-exposed patient on 20 April 2016. The analyses outlined in this protocol will not begin until after the submission of the protocol and statistical analysis plan.

7. Rationale and Background

Psoriasis is a chronic autoimmune and inflammatory disease characterized by sharply demarcated erythematous plaques that can affect any part of the body. It has a profoundly negative impact on quality of life, especially in those with moderate-to-severe disease. There is a strong genetic component and the disease may be triggered by exposure to environmental factors such as trauma to the skin (koebnerization) or streptococcal infection. Psoriasis affects approximately 3% to 4% of the population in developed countries (Rachakonda et al. 2014).

Psoriasis is associated with a number of serious comorbidities. One of the most common is psoriatic arthritis, which occurs in approximately 6% to 40% of patients with psoriasis, depending on the population studied (Kimball et al. 2008; Menter et al. 2008). Patients with psoriasis have a higher prevalence of obesity, alcohol use, and smoking than age-matched controls. Independent of these risk factors, there is an increased risk of myocardial infarctions (MIs), diabetes, hypertension, stroke, Crohn's disease, and metabolic syndrome in patients with psoriasis, particularly when the disease is severe (Yates et al. 1982; Gelfand et al. 2006; Neimann et al. 2006; Gisondi et al. 2007; Kimball et al. 2008; Ogdie et al. 2015). More recently, associations have been reported between psoriasis and other autoimmune diseases (Wu et al. 2012).

Dermatologists, regulators, and healthcare professionals have concerns about the long-term safety of biologics and other new therapies entering the market (Wan et al. 2012; Armstrong et al. 2013). In general, clinical trials capture safety data for 6 to 12 months, but the long-term safety profiles of these agents remain unclear; particularly regarding malignancies, cardiovascular events, and serious infections. While pharmaceutical companies sponsor postmarketing studies to monitor drug safety (Gottlieb et al. 2014; Luger et al. 2016), a need remains for an independent observational registry that collects and analyses longitudinal outcomes associated with psoriasis, its comorbidities and treatment, with an emphasis on malignancies, cardiovascular outcomes, and serious infections.

In 2015, Corrona and the NPF established the first US psoriasis registry co-developed and co-administered by a not-for-profit agency: the Corrona Psoriasis Registry (NPF 2015). This registry mirrors the established Corrona Rheumatoid Arthritis (RA) Registry and will be cooperatively managed by scientific, operational, and quality leaders at Corrona, and medical leaders appointed by the NPF. The purpose of this registry is to study the safety and effectiveness of biologic medications used to treat plaque psoriasis. The study is being completed to address Lilly's post-authorization regulatory requirements.

Investigators may enrol patients who have started on, or switched to, an approved systemic agent for psoriasis within the previous 12 months. All patients will receive standard-of-care treatment prescribed by the investigator, in accordance with the FDA-approved prescribing information, and all treatment decisions are the sole responsibility of the investigator. Lilly subscribes to the Corrona Psoriasis Registry in order to evaluate real-world data on the safety of ixekizumab. This protocol outlines how data obtained from this registry will be used to evaluate the safety of ixekizumab in routine clinical practice.

8. Research Question and Objectives

The primary objective of the study is to examine the incidence of malignancy, excluding NMSC, among patients with psoriasis exposed to ixekizumab in routine clinical practice relative to NBSM and non-IL-17 biologic medications used to treat psoriasis.

The secondary objective is to examine the incidence of NMSC, serious infections, opportunistic infections (including active tuberculosis), IBD, MACE, serious hypersensitivity reactions, demyelinating disease, and gastrointestinal perforation among patients with psoriasis exposed to ixekizumab in routine clinical practice relative to NBSM and non-IL-17 biologic medications used to treat psoriasis. A further objective is to obtain information about the safety of ixekizumab in the very elderly (≥75 years of age).

9. Research Methods

9.1. Study Design

This study uses prospectively collected data from the Corrona Psoriasis Registry, an existing prospective, multicentre, observational psoriasis registry, and will use a cohort study design. Longitudinal follow-up data are obtained via Corrona Psoriasis Registry questionnaires completed by both patients with psoriasis and their treating dermatologists (also known as "providers"). The registry is designed to collect data on patient demographics, smoking history, psoriasis duration, psoriasis severity, disease activity, history of prior psoriasis treatment, comorbidities, hospitalizations, TAEs, medication use, patient reported outcomes, and laboratory results.

9.2. Setting

9.2.1. Study Population

The study population includes all patients in the Corrona Psoriasis Registry, with some exclusions employed for specific analyses. Eligibility for the registry is described below, along with the current protocol's analysis-specific exclusion criteria.

9.2.2. Patient Eligibility

To be eligible for enrolment into the Corrona Psoriasis Registry, a patient must satisfy all of the inclusion criteria and must not meet any of the exclusion criteria, except where an exclusion is specified for the analysis population.

9.2.2.1. Inclusion Criteria

1. The patient has psoriasis (which may include comorbid psoriatic arthritis) diagnosed by a dermatologist.
2. The patient is at least 18 years of age or older.
3. The patient initiated a systemic psoriasis treatment within the previous 12 months. Systemic treatment includes FDA-approved biologic treatments for psoriasis and select nonbiologic treatments (methotrexate, cyclosporine, or apremilast only). Patients may have previously taken the biologic or NBSM. This will be noted in the medication history.

9.2.2.2. Exclusion Criteria

4. The patient is unable or unwilling to provide informed consent to participate in the registry.
5. The patient is restarting the same systemic medication <12 months from the previous stop.
6. The patient is participating or is planning to participate in a clinical trial.
7. The patient has a history of IL-17 inhibitor use prior to enrolment or is using a non-ixekizumab IL-17 inhibitor at enrolment (exclusion for statistical analyses of the primary objective only).

9.2.3. Duration of Study

Each patient will have the opportunity to participate in follow-up for a minimum of 8 years after the initial registry visit. Enrolment for the study is estimated to take approximately 4 years, with a total study duration of 12 years.

9.2.4. Site Selection

All sites providing data for this study will be recruited and managed by Corrona. The Corrona Psoriasis Registry estimates enrolment of approximately 200 sites across the United States and Canada (Corrona Psoriasis Registry Protocol, available on request).

9.2.5. Assessment Schedule

Enrolment date is defined as time point 0. The enrolment visit will capture information on baseline demographics, health behaviours, psoriasis duration, psoriasis severity, disease activity, history of prior psoriasis treatment, comorbidities, hospitalizations, medication use, and patient reported outcomes. Follow-up data collection should occur at 6-month follow-up visits, with a minimum time since last visit of 5 months. If the patient initiates a new psoriasis treatment less than 5 months from the previous visit, a follow-up visit should be conducted and the data collection interval will be reset. Follow-up data collection will update all baseline information and may include TAEs and laboratory test results. Adverse events (AEs) may be reported at any time during the study and are not restricted to follow-up visits.

9.2.6. Patient Withdrawal and Patients Lost to Follow-Up

If the Corrona Psoriasis Registry data cannot be collected during a 9-month period for a given patient, the site will be contacted by Corrona to encourage conducting follow-up visits when patients come to routine scheduled visits. If a 15-month period (455 days) has elapsed without the collection of data for a given patient and all reasonable attempts have been made by the site to establish contact with the patient, Corrona will ask the investigator to discontinue the patient from the registry by completing an exit questionnaire. An exit questionnaire should also be completed for any patient wishing to withdraw from the study. Once a patient has been exited from the registry, that patient is not allowed to re-enrol or to be reactivated at a later date. The patient identification will not be reused.

9.2.7. Patient Subgroups of Special Interest

This registry data will also be used to monitor the incidence of primary and secondary outcomes in very elderly patients (≥75 years of age).

9.3. Variables

During the course of routinely scheduled clinic visits, data on patient demographics, smoking history, psoriasis duration, psoriasis severity, disease activity, history of prior psoriasis treatment, comorbidities, hospitalizations, TAEs, medication use, patient reported outcomes, and laboratory results will be collected directly from patients and through providers by means of study forms. Results of diagnostic testing will also be recorded based on the availability of results from

routine clinical care. The following sections detail the variables available for this study. All information is obtained via physician and patient enrolment, follow-up questionnaires, and TAE report forms.

9.3.1. Drug Exposure

Corrona enrols patients into the registry within 12 months of starting or switching to a systemic psoriasis treatment. As a result, new medication users and continuing medication users are captured. Eligible medications for enrolment into the registry include select nonbiologic and biologic medications. Table 1 displays medications available at the time of this protocol development. Newly available psoriasis medications will be included as they are approved. Once a patient is enrolled into the registry, follow-up will occur regardless of the psoriasis treatment received, even if that treatment is not part of the eligible medications for registry enrolment. Drug utilization data are collected at each study visit.

Table 1. Eligible Medications for Enrolment into the Registry

Nonbiologic Systemic Medications	Biologic Medications*
Apremilast	Adalimumab
Cyclosporine	Brodalumab
Methotrexate	Certolizumab Pegol
	Etanercept
	Guselkumab
	Infliximab
	Ixekizumab
	Risankizumab
	Secukinumab
	Tildrakizumab
	Ustekinumab

* Eligible FDA or Health Canada-approved biologic medications at time of protocol publication.

Medications used to define the exposure cohorts are summarized in Table 2. It is important to call attention to the differences in the lists of medications between Table 1 and Table 2. These dissimilarities reflect differences between enrollment criteria (presented in Table 1) and clinical practice (presented in Table 2). For example, a patient starting cyclosporine upon registry enrolment may switch or add another medication that was not initially part of enrolment criteria. Another important difference is that non-ixekizumab IL-17 inhibitors are not included in Table 2, as they are excluded from the exposure cohort to avoid missing potential class effects. Newly approved psoriasis medications will be included as they are approved.

Table 2. Medications Included in the Nonbiologic Systemic Medication and Non-IL-17 Biologic Exposure Cohorts[a]

Nonbiologic Systemic Medications	Non-IL-17 Biologic Medications
Acitretin	Adalimumab
Apremilast	Certolizumab Pegol
Cyclosporine	Etanercept
Hydrea (hydroxyurea)	Guselkumab
Isotretinoin	Infliximab
Methotrexate	Risankizumab
Mycophenolate mofetil	Tildrakizumab
Sulfasalazine	Ustekinumab
6-thioguanine	

[a] Eligible FDA or Health Canada-approved biologic medications at time of protocol publication.

The classification of drug exposure for the evaluation of malignancy and NMSC differs from the classification used for other outcomes to accommodate the long latency of malignant outcomes even after a causal exposure. For malignancy and NMSC, assignment to exposure groups will be hierarchical. For outcomes other than malignancy, an 'as-treated' approach in which person-time accrues based on the treatment received, without regard to a hierarchy, will be used instead. The following sections outline how exposure time is defined for analyses of primary and secondary outcomes. Before analyses occur, drug exposure patterns will be examined to ensure that predefined exposure cohorts properly represent exposure in the general population. Changes to the exposure cohorts may be made to reflect real-world use.

9.3.1.1. Drug Exposure and Cohort Identification for the Primary Analysis of Malignancy and the Secondary Analysis of NMSC

For malignancy-related outcomes, follow-up time will be categorized into 3 cohorts: the NBSM cohort, the non-IL-17 biologic cohort, and the ixekizumab cohort. The exposure assignment will be hierarchical so that once exposure to a non-IL-17 inhibitor biologic occurs, time may not be attributed to the NBSM group. Similarly, once exposure to ixekizumab occurs, time may not be attributed to the other two cohorts. This approach is conservative, in that it allows attribution of malignancy events to ixekizumab, ignoring other subsequent exposures. Alternative exposure definitions will be examined in sensitivity analyses. Examination of drug exposure patterns will occur before outcomes analyses begin. An IL-17 biologic cohort will be considered if excluding patients initiating a non-ixekizumab IL-17 biologic or with a history of non-ixekizumab IL-17 biologic use results in a prohibitively small sample size.

- **NBSM cohort**: Biologic-naive NBSM users—follow-up time will begin at registry enrolment and continue until initiation of a biologic medication, end of the study period, withdrawal from the registry, incident malignancy, or death.
- **Non-IL-17 biologic cohort**: Patients using a non-IL-17 biologic medication without previous exposure to an IL-17 biologic—follow-up time will begin at registry enrolment

or subsequent non-IL-17 biologic treatment initiation and will continue until the initiation of an IL-17 inhibitor, withdrawal from the registry, incident malignancy, or death.

- **Ixekizumab cohort**: Patients exposed to ixekizumab with no prior exposure to a non-ixekizumab IL-17 inhibitor—follow-up time will begin at registry enrolment or subsequent treatment initiation and will continue until exposure to another IL-17 inhibitor occurs, end of the study period, withdrawal from the registry, incident malignancy, or death.

9.3.1.2. Drug Exposure and Cohort Identification for the Secondary Analyses of Serious Infections, Opportunistic Infections (Including Active Tuberculosis), IBD, MACE, Serious Hypersensitivity Reactions, Demyelinating Disease, and Gastrointestinal Perforation

For non-malignancy secondary outcomes, the 3 exposure cohorts described in Section 9.3.2.1 will be created; however, an as-treated approach where person-time accrues based on the treatment received will be used. The index date is the date of treatment start. A 90-day risk window will be established upon cessation of all biologic medications (Burden et al. 2012). This time will be considered "time at risk" after the medication is stopped. Follow-up time prior to registry enrolment is not used in any analysis of primary or secondary outcomes. Registry follow-up time for medications started before registry enrolment will not be used in the analysis of secondary outcomes unless the sample size becomes prohibitively small. Any follow-up time associated with the use of an IL-17 inhibitor other than ixekizumab will be excluded to allow for identification of potential class effects.

- **NBSM cohort**: Biologic naive NBSM users—follow-up time will begin at NBSM start and will continue until either the occurrence of an event, medication discontinuation, start of a biologic medication, withdrawal from the registry, or death. A new index date will be assigned when a patient switches medication within the cohort.
- **Non-IL-17 biologic cohort**: Patients starting a non-IL-17 biologic medication—follow-up will begin at treatment start and will continue until either the occurrence of an event, medication discontinuation, withdrawal from the registry, or death. A new index date will be assigned when a patient starts a medication within the cohort; concomitant use of an NBSM will be assessed and included in the analysis as a time-dependent covariate.
- **Ixekizumab cohort**: Patients starting ixekizumab—follow-up will begin at treatment start and will continue until either the occurrence of an event, medication discontinuation, withdrawal from the registry, or death. A new index date will be assigned when a patient starts a medication; concomitant use of an NBSM will be assessed and included in the analysis as a time-dependent covariate.

Simultaneous use of biologic medications is expected to be rare, as current treatment guidelines do not recommend the use of multiple biologic medications (Smith et al. 2009). Exposure time for patients with simultaneous use of ixekizumab and another biologic will be assigned to the ixekizumab cohort. A covariate will be added to the model to capture simultaneous biologic use if necessary.

9.3.1.3. Example of Exposure Classification

Patients in the Corrona Psoriasis Registry are under routine clinical care and may switch medications during the course of follow-up. This results in switching within and between the study-specific medication cohorts. Clarification of the follow-up time attribution for patients is described below.

9.3.1.3.1. Switching within an Exposure Cohort

Each patient in the registry will receive an index date representing the start of follow-up time. Information on relevant confounding variables will be collected at this time. This information is used in the propensity score analysis described in Section 9.7.3 to ensure that the exposure groups are balanced with respect to relevant confounding variables.

Drug exposure assignment will be hierarchical for malignancy outcomes (including NMSC), therefore, switching within the same cohort (NBSM or non-IL-17 biologic) will not define a new index date. Instead, the first drug use within a cohort (initiation at time of enrolment or during follow-up) will define the index date. Exposure time for the cohort will continue until a patient initiates a drug in the subsequent drug cohort. For evaluation of non-malignancy outcomes, a new index date is assigned when a patient switches medication within an exposure cohort to ensure that the patient will be re-matched with a new user in the other exposure cohort, rather than remaining matched to a continuing medication user. Follow-up time will be measured from the index date to the occurrence of an event (for time-to-event analysis), death, medication discontinuation, start of a medication for an alternate exposure cohort, or the last follow-up visit.

For biologic medication users, a 90-day risk window (or gap) will be established upon cessation of the biologic medication. This time will be considered additional "time at risk" after the medication is stopped (or during a gap up to 90 days in therapy). If a new medication is started during the 90-day window after discontinuation of a previous medication, start of the new medication will stop the 90-day risk window. Any event prior to the new medication start will be assigned to the discontinued medication. An example of the follow-up time calculation for a patient that switches medication within the non-IL-17 biologic medication cohort (non-malignancy outcome) is provided in Figure 1 in Section 9.3.1.3.3.

9.3.1.3.2. Switching between Exposure Cohorts

Switching between medication cohorts may also take place during the course of study follow-up. These switches will be handled similarly to the switches within a cohort and are demonstrated in Figure 1 in Section 9.3.1.3.3.

9.3.1.3.3. Medication Restarts

The Corrona Psoriasis Registry Protocol prohibits the enrolment of patients who are restarting a medication within the previous 12 months. Enrolments are restricted to new medication starts and patients with a maximum of 12 months of medication exposure. During the course of follow-up, patients may stop and restart medications at the discretion of their physician. Medication restarts captured within the registry will not affect the analysis of the primary outcome (malignancy), as the analytic approach for malignancies considers "ever exposure"

versus "never exposure" to ixekizumab. The analysis of secondary outcomes, however, examines treatment episodes that might include medication restarts. Patients restarting medications may have a different risk for study outcomes relative to patients who initiate or continue treatment. Therefore, patient characteristics and risk of study outcomes will be compared for those who restart medications and those who do not, to determine if it is appropriate to include both types of patients in the same analysis. If the data support analysing all treatment episodes, the following analytic approach will be taken.

- If the medication restart is within the 90-day risk window, a new index date is not assigned and follow-up time continues.
- If the restart occurs outside of the 90-day risk window, the patient will receive a new index date and will be matched to a restarter in the alternate exposure cohort.

If the data do not support analysing all treatment episodes together, patients restarting medication will be examined separately.

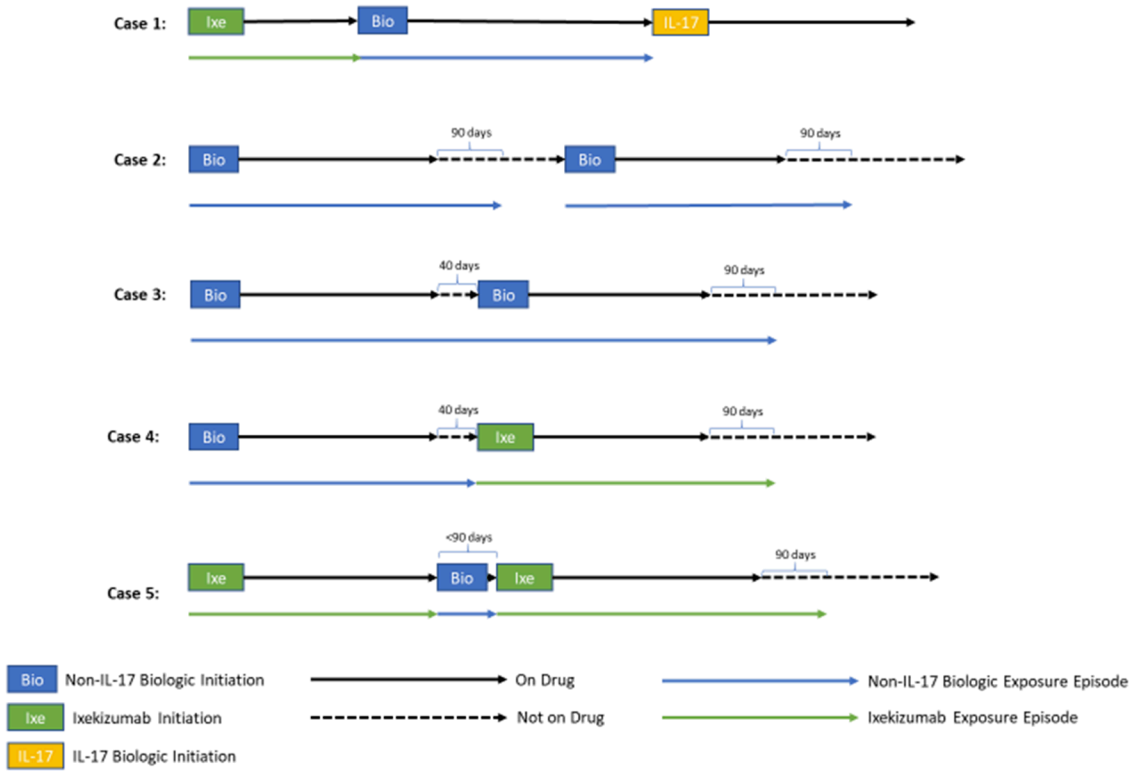

Figure 1. Example of exposure classification for non-malignancy outcomes.

Case 1 illustrates a patient contributing two exposure episodes, one to the ixekizumab cohort and one to the non-IL-17A biologic cohort. Follow-up time ends for this patient at the time of initiation of a non-ixekizumab IL-17A biologic therapy.

Case 2 illustrates a patient contributing two exposure episodes to the non-IL-17A biologic cohort. The second exposure episode is considered a medication restart, with a new index date assigned at the restart of the non-IL-17A biologic medication, because the restart occurred more than 90 days after discontinuation.

Case 3 illustrates a patient contributing one exposure episode to the non-IL-17A biologic cohort. While the patient discontinues and restarts the non-IL-17A biologic therapy, the restart occurs within 90 days of discontinuation so does not result in a separate exposure episode because a new index date is not created at medication restart.

Case 4 illustrates a patient contributing two exposure episodes, one to the non-IL-17A biologic cohort, and one to the ixekizumab cohort. The 90-day risk window after discontinuing the non-IL-17 ends at the initiation of ixekizumab. Follow-up time from ixekizumab initiation to 90 days post ixekizumab discontinuation contribute to the ixekizumab cohort.

Case 5 illustrates a patient contributing three exposure episodes, two to the ixekizumab cohort and one to the non-IL-17A biologic cohort. While ixekizumab is restarted within 90 days of discontinuation, since a non-IL-17A biologic is initiated between discontinuation and restart, a new index date is assigned and a second ixekizumab exposure episode is created.

9.3.2. Outcomes

The primary outcome of this study is malignancy, excluding NMSC. Secondary outcomes include NMSC, serious infections, opportunistic infections (including active tuberculosis), IBD, MACE, serious hypersensitivity reactions, demyelinating disease, and gastrointestinal perforation. All physician-reported malignancies will be examined in this study, with the primary analysis performed examining the events that have been adjudicated as endpoint met (probable and definite), as defined for each outcome.

Targeted events are eligible to be submitted for adjudication by trained and qualified physician reviewers once sufficiently complete with appropriate medical records to support formal evaluation of the physician-reported event and assignment of confirmation status, degree of certainty, and other relevant details pertaining to the sufficiency of reported data. Depending upon the quality and completeness of available supporting documentation, case review committees will adjudicate each event as definite, probable, possible, not an event, or records insufficient to determine whether the physician-reported event occurred as reported. Events reported as definite include supporting source data such as laboratory data, ECG tracings, procedure reports, pathology reports, or other confirmatory testing in support of the reported diagnosis. Probable events include sufficient detail and/or summarized findings by the primary source reporter (for example, specialist managing the event) to confirm that the physician-reported event was diagnosed and treated in the subject but may be missing one or more important details that would add additional confidence to the reviewer's assessment (such as primary source laboratory values or diagnostic testing results) are not available. In cases of death, for example, records of attended deaths may be available, but may not include autopsy or death certificate. In this example, cause of death may not be able to be definitively adjudicated from the available records. Events adjudicated as possible include events referenced in

supporting documentation but lacking the level of detail and/or completeness needed for reviewer confidence that the endpoint was met. Events adjudicated as possible may include events cited in an admission summary for which the subsequent chronology is unclear, conflicting, or suggestive of evolution toward an alternate diagnosis, but for which confirmatory testing results available do no provide definitive support to confirm, or rule out, despite availability of appropriate supporting documentation. Events adjudicated as not an event, are those events for which the available supporting documentation clearly refute or rule out the physician-reported diagnosis (for example, malignancy was reported but event was adjudicated as a benign tumour or pre-malignancy event instead). Adjudicators may indicate that records are insufficient to make a determination on if or when an event occurred in cases where available records are very incomplete and/or do not contain the appropriate details or data points needed to make a determination. Examples include cases where an outcome of death has been reported but the available supporting documentation ends at the point of transfer to hospice. In these instances, Corrona staff conduct site follow-up for additional documentation that may be helpful in making a definitive determination.

Corrona provides sites with training and corresponding reference table to support collection of appropriate documentation by event type (see Annex 1, Corrona Psoriasis Registry: Minimum Supporting Documentation Requirements by Targeted Event Type), as an aid for use when requesting and reviewing available supporting documentation. It is expected that supporting documents provided originate from a primary source reporter involved in the management of the reported event (vs. a note acknowledging a second-hand account by the patient alone). Various permutations of the recommended supporting documents may be submitted and deemed sufficient if they originate from a primary source and appear to correspond with the reported event of interest. Sites are queried for additional details where records are insufficient (for example, not originating from a primary source) or do not appear to be the correct/corresponding records for the reported event (for example, supporting documents belonging to another subject or event inadvertently appended).

Adjudication procedures require exposure-blind and cohort-blind assessment by adjudicators. Corrona case processing staff are required to redact details regarding current and prior exposure to medications for the disease under study as a standard step in the workflow for preparing case dossiers for assignment to the appropriate adjudication committee (by event type). Details regarding cohort allocation are not shared with registry adjudication committees.

The following sections describe each outcome.

9.3.2.1. Malignancy, Excluding NMSC

Cases of malignancy are captured by physician reports and include skin cancers, solid cancers, and hematologic cancers. Validation of incident malignancies within the Corrona RA Registry has been described previously (Fisher et al. 2012), and is the same process implemented within the Corrona Psoriasis Registry. Briefly, physicians are required to complete a TAE form for each report of incident malignancy, and to request source documentation including pathology reports, hospital discharge summaries, notes from an oncologist, and/or notes from a primary

care physician, so that each case may be adjudicated as definite, probable, possible, not a malignancy, or records insufficient for confirmation of physician-reported malignancy.

The subset of physician-reported malignancy events that are complete with supporting documentation that have been adjudicated as definite or probable malignancy events will be examined in this study. All physician-reported malignancy events will be examined in a sensitivity analysis.

9.3.2.2. NMSC

Cases of NMSC are captured by physician reports. Validation of NMSC follows the same process as the malignancies described above. Briefly, physicians are required to complete a TAE form for each report of incident malignancy, and to request source documentation including pathology reports, hospital discharge summaries, notes from an oncologist, and/or notes from a primary care physician, so that each case may be adjudicated as definite, probable, possible, not a malignancy, or records insufficient for confirmation of physician-reported malignancy.

The subset of physician-reported NMSC events that are complete with supporting documentation that have been adjudicated as definite or probable NMSC events will be examined in this study. All physician-reported NMSC will be examined in a sensitivity analysis.

9.3.2.3. Serious Infections

Serious infections are captured by physician reports and include infections requiring or prolonging hospitalization; life-threatening infections and infections leading to death; infections causing disability; permanent damage or congenital abnormality; infections requiring parenteral or intravenous antibiotics. The subset of physician-reported serious infection events that are complete with supporting documentation that have been adjudicated as definite or probable serious infection will be examined in this study. All physician-reported serious infections events will be examined in a sensitivity analysis.

Validation of physician-reported serious infection events within the Corrona RA Registry has been described previously (Curtis et al. 2009), and is the same process implemented within the Corrona Psoriasis Registry. Briefly, physicians are required to complete a TAE form for each reported serious infection, and to request source documentation (for example, hospital records, pathogen testing) so that each case may be adjudicated as: 1) confirmed, empirically treated (for example, there was evidence that the physician was treating an infection, but no definitive information such as positive microbial cultures was identified); 2) possible (that is, there may have been an infection, but the evidence was limited); 3) unlikely (that is, minimal or no supporting evidence for report of infection, based on available medical records); or 4) available medical records insufficient for confirmation of physician-reported serious infection. Pre-specified serious infections of interest include cellulitis, pneumonia, meningitis, osteomyelitis, septic arthritis, pyelonephritis, and infections associated with severe inflammatory response syndrome. Discussion of how these infections will be analysed is provided in Section 9.7.7.2.

9.3.2.4. Opportunistic Infections

The occurrence of opportunistic infections is collected via physician follow-up forms and TAE forms. Opportunistic infections identified from TAE forms will be serious infections as defined in Section 9.3.2.3. The subset of physician-reported opportunistic infections that are complete with supporting documentation that have been adjudicated as definite or probable opportunistic infection will be examined in this study. All physician-reported opportunistic infection events will be examined in a sensitivity analysis.

Nonserious opportunistic infections are identified from physician follow-up forms. Prespecified opportunistic infections of interest include, but are not limited to, infections due to *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Mycobacterium tuberculosis (active vs. Latent infections)*, *Pneumocystis jirovecii*, herpes zoster and certain other microorganisms, and invasive infections due to *Listeria monocytogenes*, *Salmonella*, herpes simplex virus, *Candida (reported candidiasis events are sub-classified as oropharyngeal, intertriginous, cutaneous, disseminated, or genital/vulvovaginal)* and certain other microorganisms. Pathogen codes are collected for all infection events, where data are available. It should be noted that pathogen testing results are not consistently available in routine care and management of infection, particularly for cases of non-serious infection. To the extent that these data are available for non-serious infection, pathogen codes will be used to differentiate opportunistic from non-opportunistic infections. Non-serious infections are not required to be reported via TAE, so supporting medical records will not be available for formal review and adjudication for most non-serious infection events. Discussion of the analysis is provided in Section 9.7.7.3.

9.3.2.5. Inflammatory Bowel Disease

The Corrona Psoriasis Registry implemented a TAE form for capture of IBD on 16 June 2017. This form captures incident and worsening cases of Crohn's disease, ulcerative colitis, and indeterminate IBD. Physicians are required to complete this form for each case of incident disease or flare (worsening). Physicians are also required to request source documentation so that each suspected physician-reported IBD event may be adjudicated in order to render an assessment as to whether the case represents one of the following EPIMAD (Register **EPI**demiologique des **M**aladies de l'**A**ppareil **D**igestif) criteria: 1) Definite Event (counts as a confirmed event); 2) Probable Event (counts as a confirmed event); or 3) Possible Event (does not count as a confirmed event). Additionally, the adjudicators have the following choices: 4) Not consistent with IBD (does not meet the event definition and likely represents an alternative or non-event diagnosis); and 5) Lacks sufficient documentation for confirmation of an IBD event (composite endpoint of Crohn's disease and ulcerative colitis) (Gower–Rousseau et al. 1994). If there are sufficient numbers of cases, Crohn's disease and ulcerative colitis may be examined separately.

The subset of physician-reported IBD events (new onset or flares) that are complete with supporting documentation that have been adjudicated as definite or probable IBD will be examined in this study. All physician-reported IBD events will be examined in a sensitivity analysis.

9.3.2.6. Major Adverse Cardiovascular Events

MACE is a composite cardiovascular endpoint that includes fatal and nonfatal MI, fatal or nonfatal ischemic stroke, and cardiovascular death. Incident MACE are identified by a physician report on a TAE form. The subset of physician-reported MACE events that are complete with supporting documentation that have been adjudicated as definite or probable MACE will be examined in this study. All physician-reported MACE events will be examined in a sensitivity analysis.

Validation of MACE within the Corrona RA Registry has been described previously (Solomon et al. 2010), and is the same process implemented within the Corrona Psoriasis Registry. Briefly, physicians are required to complete a TAE form for each report of MACE, and to request source documentation (for example, hospital records). These source documents are sent to Corrona so that each case may be adjudicated by an independent committee as definite, probable, possible, not an event, or available records insufficient for confirmation of physician-reported MACE. Definitive validation of the event occurs when available supporting records are adequately complete and clearly document a diagnosis that meets case definition criteria for reporting as a MACE, without qualifiers or descriptions of alternate aetiology to explain the reported signs and symptoms. MACE are adjudicated in accordance with American College of Cardiology/American Heart Association guidance (Hicks et al. 2015).

9.3.2.7. Serious Hypersensitivity Reactions

Cases of serious hypersensitivity reactions are captured by physician reports and include reactions that require or prolong hospitalization, are life-threatening or lead to death, or cause disability or permanent damage. The subset of physician-reported serious hypersensitivity reaction events that are complete with supporting documentation that have been adjudicated as definite or probable serious hypersensitivity reaction will be examined in this study. All physician-reported serious hypersensitivity events will be examined in a sensitivity analysis.

Physicians are required to complete the TAE form and request source documentation so that reported cases can be adjudicated as definite, probable, possible, not an event, or available records insufficient for confirmation of physician-reported serious hypersensitivity reactions. Definitive validation of the event occurs when available supporting records are adequately complete and clearly document a diagnosis that meets case definition criteria for reporting as a serious hypersensitivity reaction, without qualifiers or descriptions of alternate aetiology to explain the reported signs and symptoms.

9.3.2.8. Demyelinating Disease

Cases of demyelinating disease are captured by physician report and include progressive multifocal leukoencephalopathy (also analysed as an opportunistic infection), demyelinating disease, or other serious neurological conditions (for example, amyotrophic lateral sclerosis). The subset of physician-reported demyelinating disease events that are complete with supporting documentation that have been adjudicated as definite or probable demyelinating disease will be examined in this study. All physician-reported demyelinating disease events will be examined in a sensitivity analysis.

Physicians are required to complete the TAE form and request source documentation so that reported cases can be adjudicated as definite, probable, possible, not an event, or available records insufficient for confirmation of physician-reported demyelinating disease. Definitive validation of the event occurs when available supporting records are adequately complete and clearly document a diagnosis that meets case definition criteria for reporting as a demyelinating disease, without qualifiers or descriptions of alternate aetiology to explain the reported signs and symptoms.

9.3.2.9. Gastrointestinal Perforations

The Corrona Psoriasis Registry captures physician-reported gastrointestinal perforations on TAE forms. The subset of physician-reported gastrointestinal perforation events that are complete with supporting documentation that have been adjudicated as definite or probable gastrointestinal perforation will be examined in this study. All physician-reported gastrointestinal perforation events will be examined in a sensitivity analysis.

Physicians are required to complete the TAE form and request source documentation so that reported cases can be adjudicated as definite, probable, possible, not an event, or available records insufficient for confirmation of physician-reported gastrointestinal perforation. Definitive validation of the event occurs when available supporting records are adequately complete and clearly document a diagnosis that meets case definition criteria for reporting as a gastrointestinal perforation, without qualifiers or descriptions of alternate aetiology to explain the reported signs and symptoms.

9.3.3. Covariates

In addition to TAEs, Corrona also captures a variety of other patient information including demographics; medical history and comorbidities; health behaviours; and psoriasis disease duration, severity, and treatment. The covariates listed in Table 3 will be considered in the analyses for their potential to confound the association between exposure and TAE outcome. Further explanation is provided in Section 9.4.

Table 3. Baseline Covariates for Consideration in Each Outcome-Specific Analysis

Outcome	Baseline Covariates for Consideration in the Propensity Score Model
Malignancy, excluding NMSC, and NMSC	Age, sex, race, body mass index, alcohol use, smoking, education, psoriasis disease severity (BSA), psoriasis disease duration, previous ultraviolet therapy, modified Charlson Comorbidity score, personal history of cancer (excluding NMSC) ≤1 year prior to or including the index date, personal history of cancer (excluding NMSC) > 1 year prior to index date, personal history of NMSC, active NMSC, family history of NMSC, previous history of biologic medication use
Serious and opportunistic infection	Age, sex, race, body mass index, alcohol use, smoking, education, psoriasis disease severity (BSA), psoriasis disease duration, diabetes mellitus, chronic lung disease, liver disorder, ischemic heart disease, congestive heart disease, periodontal disease, previous serious infection, previous NBSM use, previous non-ixekizumab biologic use
Inflammatory bowel disease	Age, sex, race, body mass index, alcohol use, smoking, education, psoriasis disease severity (BSA), psoriasis disease duration, nonsteroidal anti-inflammatory medication use, previous IL-17 inhibitor use, previous IBD flare, family history of IBD, perianal pain and perianal bleeding
Major adverse cardiac event	Age, sex, race, body mass index, alcohol use, smoking, education, psoriasis disease severity (BSA), psoriasis disease duration, history of cardiovascular disease (MI, stroke, unstable angina, hospitalized for congestive heart failure, ventricular arrhythmia, cardiovascular revascularization procedure, coronary artery disease, and transient ischemic attack), diabetes mellitus, physician-reported history of hypertension, hyperlipidemia, aspirin use, lipid lowering agent use, antiplatelet agent use, parent with a heart attack before age 65
Serious hypersensitivity reaction	Age, sex, race, body mass index, alcohol use, smoking, education, psoriasis disease severity (BSA), psoriasis disease duration, asthma
Demyelinating disease	Age, sex, race, psoriasis disease severity (BSA), psoriasis disease duration, previous exposure to TNF-α inhibitor, history of demyelinating disease
Gastrointestinal perforation	Age, sex, race, body mass index, psoriasis disease severity (BSA), psoriasis disease duration, nonsteroidal anti-inflammatory medication, history of diverticulitis, proton pump inhibitor use, IBD

Abbreviations: BSA = body surface area; IBD = inflammatory bowel disease; IL-17 = interleukin-17; MI = myocardial infarction; NBSM = nonbiologic systemic medication; NMSC = non-melanoma skin cancer; TNF-α = tumour necrosis factor alpha.

9.4. Data Sources

The data for this study will be obtained from the Corrona Psoriasis Registry. This registry was selected for the high quality, longitudinal, comprehensive data capture on adult patients starting on or switching to an FDA-approved biologic or nonbiologic treatment for psoriasis (nonbiologics include methotrexate, cyclosporine, or apremilast only). Exposures, outcomes, and covariates are reported directly by patients and physicians and are collected at baseline and each follow-up visit. Table 4 presents the Corrona medical review processes as described in the applicable Corrona procedural documents:

Table 4. Corrona Medical Review Processes

Document Title	Document Type	Document Number
Targeted Adverse Event (TAE) Reporting	Standard Operating Procedure	PV-600
Investigator TAE Reporting Requirements	Work Instruction	PV-60-00
Targeted Event Reporting Guidelines	Site Reference	PV-60-00-GD1
Minimum Supporting Documentation Requirements by TAE Type	Site Reference	PV-60-00-T1
Targeted Adverse Event (TAE) Intake	Work Instruction	PV-60-01
TAE Quality Control and Data Management	Work Instruction	PV-60-02
Case Adjudication Assignment and Tracking	Work Instruction	WI-PV-60-03
Case Adjudication Completion	Work Instruction	WI-PV-60-04

9.5. Study Size

Sample size and power calculations were performed using the background incidence rate of malignancy to ensure that the registry will adequately detect a 1.5-fold increase in the risk of malignancy, excluding NMSC, among the ixekizumab-treated cohort relative to patients in the non-IL-17 biologic cohort. The following assumptions were made for the calculations:

Power and sample size calculations for the primary endpoint was based on the method developed by Thode (1997) on testing differences between 2 Poisson rates with the following assumptions:

1. One-sided Type I error rate of 0.05 (Thode 1997)
2. Background incidence rate of malignancy, excluding NMSC: 0.61 per 100 patient-years (Papp et al. 2012)
3. 10.0% annual attrition rate.

The Corrona Psoriasis Registry estimates that it will take approximately 4 years to achieve full enrolment (4000 ixekizumab-treated patients and a minimum of 4000 non-IL-17 comparator patients). With 4000 ixekizumab-treated patients and 4000 non-IL-17 comparator patients, the study will achieve 80% power to detect a 1.5-relative rate of malignancy after all patients achieve at a minimum of 3 years of follow-up during the 12-year study. The actual total follow-up time among accrued patients will be calculated at the time of the interim report and the time of the final report to determine whether sufficient total follow-up time has accrued to achieve adequate (at least 80%) power given an assumed event rate.

9.6. Data Management

Refer to the current version of the Corrona Psoriasis Registry Protocol for details related to data management for this study.

9.6.1. Data to be Collected

Refer to Section 9.3 for information about data to be collected.

9.6.1.1. Missing Data

For outcome variables and safety events, no imputation of missing data will be conducted before modelling the data. If the missing data for a particular variable exceeds 15%, imputation of the missing values for the adjusting variables will be considered before modelling the data. If imputation is deemed necessary, multiple imputation by chained equations (MICE) will be considered (Royston 2004). This is a multiple multivariate imputation method that is described by van Burren et al. (1999) and is implemented in Stata (StataCorp LP, College Station, TX) in a series of macros (Royston and White 2011). Other methods will be considered as needed.

9.7. Data Analysis

All protocols for comparative research are subject to Corrona approval and will be executed by Corrona statisticians. Analyses will be conducted separately for each outcome and will include descriptive analyses, comparative analyses (where appropriate), and any relevant sensitivity analyses. Propensity scores will be used to address imbalances in the patient population that may confound the association between treatment and study outcomes. For all analyses, ixekizumab will be the treatment of interest. The NBSM cohort and the non-IL-17 biologic cohort will be the reference groups. The number of NBSM medication users is expected to be small. Comparisons with this group of patients is intended to provide information about the potential risk of secondary outcomes associated with ixekizumab that may not be found with a comparison to other biologic medication; however, these analyses will be exploratory given the limited number of NBSM users expected in the registry.

When 4000 ixekizumab patients have accrued, the total person-years of follow-up will be computed for both the malignancy exposure cohorts and the non-malignancy exposure cohorts. For each outcome, we will determine whether the accrued person-time yields adequate power (at least 80% power) to detect an increased risk of 1.5 or greater. For outcomes with adequate power at the time of the interim report, a comparative analysis will be performed between the cohorts. For outcomes with less than adequate power, only descriptive analyses will be included in the interim report. Final analyses of all outcomes (regardless of whether an interim comparative analysis was performed) will begin 8 years after the last patient enrols. A statistical analysis plan (SAP) will be submitted to the FDA prior to the start of the analysis.

9.7.1. Analysis Population

The analysis population for all outcomes includes all patients with outcome information who have given informed consent, are enrolled in the Corrona Psoriasis Registry, and whose follow-up time is included in the drug exposure groups defined in Section 9.3.1. The primary analysis will include registry follow-up time for medications initiated at or after enrolment as well as medications initiated within the past 12 months prior to registry enrolment. The secondary analysis will include registry follow-up time only for medications started at or after enrolment. For a given outcome, patients who experience an event but do not have sufficient supporting documentation to undergo adjudication of the event will be excluded from the analysis (both the event and associated follow-up time). Subgroup analyses will be performed on patients of

special interest if there is sufficient sample size. Sample size and statistical power in these subgroup analyses may be limited.

9.7.2. Background and Rationale for Propensity Scores

Drug exposure in pharmacoepidemiological studies does not occur at random and is a result of patient, physician, and system-related factors. When these factors are associated with the outcome of interest, comparisons of different drug exposure cohorts will be confounded due to channelling bias. Propensity scores address this imbalance by providing a mechanism to compare patients with concordant baseline risk but discordant exposure (Schneeweiss 2007). For clarity, covariates included in the propensity score models are also referred to as confounders because they confound the association between exposure and outcome.

9.7.3. Propensity Score Definition and Estimation

A propensity score is an estimate of the probability that a patient receives a particular treatment, conditional on measured characteristics at the time a treatment decision is made (Rosenbaum and Rubin 1983). For this study, a patient's propensity score will reflect the predicted probability of exposure given his or her characteristics at the index date. Propensity scores will be estimated using logistic regression models predicting the probability of ixekizumab exposure compared to the other exposure groups (NBSM users and non-IL-17 biologic medication users). These models will be constructed separately for new and continuing users, and for each primary and secondary outcome (Section 9.3.2). The models will include variables that are known risk factors for safety outcomes and associated with systemic treatments for psoriasis. Covariates considered for inclusion in the propensity score models are provided in Table 3. To account for temporal variability in prescribing patterns, the propensity score models will be estimated within blocks of calendar time. The inclusion of interaction and nonlinear terms will be guided by clinical judgement. Evaluation of the propensity score models is discussed in Section 9.7.3.

Newly marketed drugs often experience changes in prescribing patterns over time so that a patient characteristic that was once associated with treatment selection becomes more or less relevant over the drug's lifecycle. A particularly dynamic time in the lifecycle of a new drug is the time between marketing authorization and the stabilization of use patterns, market share, and insurance coverage (Schneeweiss et al. 2011). To account for this, a calendar specific propensity score will be employed, as described by Mack et al. (2013) and Seeger et al. (2003). These methods estimate the propensity score models and time or match exposure episodes within blocks of calendar time to account for temporal variability in prescribing patterns.

9.7.4. Using the Propensity Score to Account for Channelling Bias

Each patient in the study will have at least 1 estimated propensity score that represents the probability of exposure at index date, given baseline characteristics (new medication starts will be considered a new index date). Trimming for common support, matching and stratification on the propensity score is relatively straightforward with 2 exposure groups, but becomes increasingly complex as the number of exposure groups increases. Multiple exposure groups and the limited registry sample available for this study mean that matching may result in a high

number of unmatched patients and stratification may result in strata with few or no patients. Therefore, this study will examine pairwise comparisons of exposure cohorts: the ixekizumab cohort versus the non-IL-17 biologic cohort, and the ixekizumab cohort versus the NBSM cohort. For each comparison, new and continuing users in the ixekizumab exposure cohorts will be evaluated separately among new and continuing users in the comparator exposure cohorts.

Propensity score trimming for common support will be the primary approach and propensity score matching will be used as a sensitivity analysis (as the number of matched patients may be prohibitively small). Propensity score trimming for common support and matching will be performed using objective algorithms and will be discussed further in the SAP. The effectiveness of the propensity score approach will be evaluated and the propensity score model will be adjusted as appropriate. The propensity score model and approach will be finalized before initiating any safety outcomes analyses.

9.7.5. Evaluation of the Propensity Score Model and Stratification

Before initiating the outcome analysis, the ability of the propensity score stratification to balance the distribution of baseline confounders and reduce channelling bias will be evaluated.

The appropriateness of the propensity score modelling is judged by whether balance on pretreatment characteristics is achieved between the treatment and reference groups (D'Agostino and D'Agostino 2007; Rubin 2007; Spreeuwenberg et al. 2010). Standardized differences will be used to assess differences between the cohorts across all measured baseline covariates before and after propensity score trimming. As a rule, standardized differences greater than 0.10 indicate an imbalance that may require further investigation (Austin 2011). Higher-level terms or interactions may be considered when a variable is unbalanced across the ixekizumab and reference cohorts, or when informed by clinical judgement (for example, an interaction between age and sex for MACE outcomes). Any covariates not balanced after applying propensity score method will be included in the Cox model.

9.7.6. Primary Analysis

The outcome for the primary analysis is all malignancies, excluding NMSC, adjudicated as probable or definite. Patients with a physician-reported event but without adequate supporting documentation available will be excluded from the analysis (along with their associated follow-up time), as they are not able to undergo event adjudication. Malignancy outcomes require a long latency period, and as a result, are not easily attributed to a particular drug exposure. To account for this ambiguity, the primary analysis will consider the risk of malignancy associated with ever use of ixekizumab. The rate of malignancy will also be monitored in very elderly patients (≥75 years of age; Section 9.3.2.1).

Entry into a treatment cohort is considered baseline and can occur at enrolment or upon initiation of a non-IL-17 biologic or ixekizumab during follow-up (see Section 9.3.1). A number of descriptive statistics and crude rates will be generated to understand the registry data before comparative analyses begin:

- Number of people with past ixekizumab or non-ixekizumab IL-17 biologic use at baseline
- Baseline demographic and clinical characteristics and standardized differences for the NBSM, non-IL-17 biologic, and ixekizumab cohorts (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients)
- Description of psoriasis treatments in each cohort and median duration of exposure of each treatment
- The distribution of medication initiations prior to enrolment versus at or after enrolment at baseline.
- Number of people with a history of malignancy at baseline (≤1 year prior to and including the index date and >1 year prior to index date) for each exposure cohort
- Distribution of follow-up time for NBSM, non-IL-17 biologic and ixekizumab cohorts (all patients, propensity trimmed cohorts and propensity matched patients, and unmatched patients)
- Crude malignancy incidence rate by duration of exposure
- Pattern of medication use post-index date for the ixekizumab, non-IL-17 biologic, and NBSM cohorts (all patients, propensity trimmed cohorts and propensity matched patients, and unmatched patients)
- Distribution of time to first malignancies, excluding NMSC, and malignancy by type for the ixekizumab, non-IL-17 biologic, and NBSM cohorts (all patients, propensity trimmed cohorts and propensity matched patients, and unmatched patients)

After descriptive statistics are calculated, calendar time specific propensity score methods will be used as described in Section 9.7.4. No comparative analyses will begin until finalization of the exposure cohorts and propensity score models are achieved.

Cox proportional hazards regression models will be used to estimate the HRs and 95% confidence intervals (CIs) of malignancies among patients in the ixekizumab cohort versus the non-IL-17A biologic cohort; and the ixekizumab cohort versus the NBSM cohort (null hypothesis [H_0]: HR=1). The model will contain exposure cohort, any variables that remain unbalanced after propensity score methods are applied (Table 3), and a time-dependent variable capturing concomitant psoriasis treatment. Methods to account for within patient correlation will be examined and employed. In the sensitivity analyses using a matched population, a sandwich variance estimator will be used to account for the matched data. Model diagnostics will be performed to identify any influential observations. These analyses may be modified to focus on the class of IL-17A inhibitors rather than ixekizumab if capturing ever exposure to ixekizumab without other IL-17A inhibitor use is infeasible. Sensitivity analyses will be performed accordingly and are discussed in Section 9.7.8 .

9.7.7. Secondary Analyses

Secondary analyses will be performed for NMSC, serious infections, opportunistic infections (including active tuberculosis), IBD, MACE, serious hypersensitivity reactions, demyelinating disease, and gastrointestinal perforation. Except for the analysis of NMSC, the secondary analysis will only consider medication starts that occur at or after enrolment (unless the sample

size is prohibitively small). For the NMSC outcome, the analysis population will consist of exposure time while on the registry for medication initiations that occur prior to enrolment as well as exposure time with on the registry for medication initiations that occurred at or after registry enrolment (in a similar fashion to the malignancy evaluation). Events and associated follow-up time without sufficient supporting documentation will be excluded from analysis of secondary outcomes. The rate of secondary outcomes will be monitored in very elderly patients (≥75 years of age; Section 9.2.7). Before beginning comparative analyses, a number of descriptive statistics and crude rates will be generated to understand the registry data. Baseline is defined as entry into the treatment cohort, whether that be registry enrolment date for medication initiations prior to registry enrolment (only if included due to sample size) and treatment start date for medication started at or after registry enrolment:

- Baseline demographic and clinical characteristics and standardized differences for the NBSM cohort, non-IL-17A biologic cohort, and the ixekizumab cohort (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients)
- Number of patients with a history of the secondary outcome at baseline
- Distribution of follow-up time for the NBSM cohort, non-IL-17A biologic cohort, and the ixekizumab cohort (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients)
- Crude rate of secondary outcomes stratified by time of exposure
- The number of new medication starts for trimmed populations (and matched populations in the sensitivity analysis) within the NBSM cohort, non-IL-17A biologic cohort, and the ixekizumab cohort

Comparative analyses will be implemented, using calendar time propensity score methods to control for confounding. Model diagnostics will be performed on all models to identify any influential observations. Sensitivity analyses will be performed accordingly. No comparative analyses will begin until finalization of the exposure cohorts and propensity score models are achieved. Details of outcome-specific analyses are presented below.

9.7.7.1. NMSC

The outcome for this analysis is probable and definite NMSC as defined in Section 9.3.2.2. All patients and associated follow-up time with a physician-reported NMSC without adequate supporting documentation for undergoing adjudication will be excluded. In addition to the descriptive statistics and crude rates described in Section 9.7.7, analysis of NMSC will include:

- History of NMSC at baseline (baseline is same as for malignancy outcomes), overall and by whether the medication initiation was prior to enrolment versus at or after enrolment
- Distribution follow-up time for the NBSM, non-IL-17A biologic, and ixekizumab cohorts (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients)

- Pattern of medication use postindex date for the ixekizumab, non-IL-17A biologic, and NBSM cohorts (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients)
- Distribution of time to first NMSC event for the ixekizumab, non-IL-17A biologic, and NBSM cohorts (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients)

After descriptive statistics are calculated, calendar-specific propensity score methods will be used as described in Section 9.7.4. No comparative analyses will begin until finalization of the exposure cohorts and propensity score models are achieved.

Cox proportional hazards regression models will be used to estimate the HRs and 95% CIs of newly diagnosed NMSC among patients in the ixekizumab cohort versus the non-IL-17 biologic cohort and the ixekizumab cohort versus the NBSM cohort. The model will contain exposure cohort, any variables that remain unbalanced after propensity score methods are applied (Table 3), and a time-dependent variable capturing concomitant psoriasis treatment. In the sensitivity analysis using matched cohorts, a sandwich variance estimator will be used to account for the matched data, and methods used to account for within patient correlation will be examined. Patients will be censored at the end of the study period, development of NMSC, withdrawal from the registry, or death. Model diagnostics will be performed to identify any influential observations. These analyses may be modified to focus on the class of IL-17 inhibitors rather than ixekizumab if capturing ever exposure to ixekizumab without other IL-17 inhibitor use is infeasible.

9.7.7.2. Serious Infections

The outcome for this analysis is first serious infection as defined in Section 9.3.2.3.

In addition to the descriptive statistics and crude rates described in Section 9.7.7, analyses of serious infections will include:

- Distribution of time to first serious infection for the NBSM cohort, non-IL-17 biologic cohort, and the ixekizumab cohort (all patients, propensity trimmed cohorts and propensity matched patients, and unmatched patients)
- Crude rate of first serious infection and first serious infection by site of infection and for the prespecified infections (Section 9.3.2.3), per 100 patient-years, for the NBSM cohort, non-IL-17A biologic cohort, and the ixekizumab cohort (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients); within cohorts, stratified by concomitant disease-modifying anti-rheumatic drug (DMARD) use
- The distribution of the number of serious infections per patient

Patients and their associated follow-up time with a physician-reported serious infection without adequate supporting documentation for undergoing adjudication will be excluded. Propensity scores methods will be used as described in Section 9.7.4. Cox proportional hazards regression will be used to compare the rate of first serious infection between the ixekizumab and NBSM cohorts, and the ixekizumab and non-IL-17 biologic cohorts. All models will include the

exposure cohort, concomitant NBSM use, and any variables that remain unbalanced after propensity score methods are applied (Table 3), and a time-dependent variable capturing concomitant psoriasis treatment. In the sensitivity analysis using matched cohorts, a sandwich variance estimator will be used to account for the matched data and methods used to account for within-patient correlation will be examined. Exposure time will be censored at the end of the study period, 90 days following discontinuation of a medication or switching to a medication in an alternate exposure cohort, withdrawal from the registry, first serious infection, or death.

Proportional hazards of the exposure groups will be evaluated using Kaplan-Meier survival curves. If the proportional hazards assumption is violated, other models that relax the proportional hazards assumption will be considered. An analysis of the total number of serious infections (not just the first serious infection per exposure episode) will also be given and is described in Section 9.7.8.4.

9.7.7.3. Opportunistic Infections

The Corrona Psoriasis Registry does not request source documents or adjudicate nonserious outcomes. Therefore, source documentation requests and adjudication will only be performed for serious opportunistic infections.

To account for differences in the level of certainty around serious and nonserious opportunistic infections, 2 secondary analyses will be performed: an analysis of confirmed and empirically treated first serious opportunistic infection and an analysis of all first opportunistic infections, irrespective of seriousness.

The outcomes for this analysis are first serious opportunistic infection, and first opportunistic infection irrespective of seriousness for a parallel analysis as defined in Section 9.3.2.4.

In addition to the descriptive statistics and crude rates described in Section 9.7.7, analyses for opportunistic infections will include the following for first serious opportunistic infection and first opportunistic infection, regardless of seriousness.

- Distribution of time to first opportunistic infection for the NBSM cohort, non-IL-17 biologic cohort, and the ixekizumab cohort (all patients, propensity trimmed cohorts and propensity matched patients, and unmatched patients)
- Crude rate of the first opportunistic infection, the first opportunistic infection by type, and the first prespecified opportunistic infection (Section 9.3.2.4) per 100 patient-years, for the NBSM cohort, non-IL-17 biologic cohort, and the ixekizumab cohort (all patients, propensity trimmed cohorts and propensity matched patients, and unmatched patients) within cohorts, stratified by concomitant DMARD use
- The distribution of the number of opportunistic infections per patient
- The distribution of serious and nonserious opportunistic infections

Patients and their associated follow-up time with a physician-reported serious opportunistic infection without adequate supporting documentation for undergoing adjudication will be excluded. Propensity score methods will be used as described in Section 9.7.4. Cox

proportional hazards regression will be used to compare the rate of first opportunistic infection between the ixekizumab and NBSM cohorts, and the ixekizumab and non-IL-17 biologic cohorts. All models will include the exposure cohort, concomitant NBSM use, and any variables that remain unbalanced after propensity score methods are applied (Table 3), and a time-dependent variable capturing concomitant psoriasis treatment. In the sensitivity analysis using matched cohorts, a sandwich variance estimator will be used to account for the matched data, and methods used to account for within-patient correlation will be examined. Exposure time will be censored at end of the study period, 90 days following discontinuation of a medication or switching to a new medication in an alternate cohort, at withdrawal from the registry, first opportunistic infection, or death. These analyses will be performed for first serious opportunistic infections and for first opportunistic infections regardless of seriousness.

Proportional hazards of the exposure groups will be evaluated using Kaplan-Meier survival curves. If the proportional hazards assumption is violated, other models that relax the proportional hazards assumption will be considered. Another analysis that includes subsequent opportunistic infections will also be performed and is described in Section 9.7.8.5.

9.7.7.4. Inflammatory Bowel Disease

Two outcomes will be considered for the analysis of IBD: time until incident diagnosis of IBD (only among patients without preexisting IBD) and time until first flare among patients with existing IBD (Section 9.3.2.5). For the analysis of time until first flare, the index date will be the date of the preceding IBD event. Because several medications included in the comparator cohort (non-IL-17a biologic cohort) are approved for the treatment of IBD, we will limit the comparison cohort when evaluating IBD outcomes. Specifically, the ixekizumab cohort will be compared only to the subset of patients receiving non-IBD medications in the non-IL-17 biologic cohort (currently only etanercept, which is not approved for the treatment of IBD).

In addition to the descriptive statistics and crude rates described in Section 9.7.7, analyses for IBD will include:

- Distribution of time to first diagnosis of IBD for the NBSM cohort, non-IBD medications in the non-IL-17A biologic cohort and the ixekizumab cohort (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients)
- Distribution of time until first IBD flare among patients with prevalent (existing) IBD for the NBSM cohort, non-IBD medications in the non-IL-17A biologic cohort, and the ixekizumab cohort (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients)
- Crude rate of incident IBD diagnosis, per 100 patient-years, for the NBSM cohort, non-IBD medications in the non-IL-17A biologic cohort, and the ixekizumab cohort (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients); within cohorts, stratified by concomitant DMARD use
- Crude rate, per 100 patient-years, of incident flare among patients with prevalent IBD in the NBSM cohort, non-IBD medications in the non-IL-17A biologic cohort, and the ixekizumab cohort (all patients, propensity trimmed populations and propensity

matched populations, and unmatched patients); within cohorts, stratified by concomitant DMARD use
- The number of total IBD events per patient (incident IBD and flare)
- The distribution of Crohn's disease and ulcerative colitis among patients with IBD

Any patient (and their associated follow-up time) with a physician-reported IBD event without adequate supporting documentation for undergoing adjudication will be excluded from all analyses of IBD. Propensity scores methods will be used as described in Section 9.7.4. Cox proportional hazards regression models (with separate propensity score matching) will be used to compare the rate of incident IBD diagnosis and incident IBD flares between the ixekizumab and NBSM cohorts, and the ixekizumab and non-IBD medications in the non-IL-17 biologic cohorts. All models will include the exposure cohort, concomitant NBSM use, and any variables that remain unbalanced after propensity score methods are applied (Table 3), and a time-dependent variable capturing concomitant psoriasis treatment. In the sensitivity analysis using matched cohorts, a sandwich variance estimator will be used to account for the matched data and methods used to account for within-patient correlation will be examined. Exposure time will be censored at the end of the study period, 90 days following discontinuation of a medication or switching to a new medication, at withdrawal from the registry, the development of IBD for the analysis of incident IBD diagnosis, the first flare for analysis of time until first flare, or death. A patient who develops IBD during the course of the study will be eligible for the analysis of first flare. If there are a sufficient number of cases, Crohn's disease and ulcerative colitis will be examined separately.

Proportional hazards of the exposure groups will be evaluated using Kaplan-Meier survival curves. If the proportional hazards assumption is violated, other models that relax the proportional hazards assumption will be considered. An analysis that allows for multiple flares will also be performed and is described in Section 9.7.8.6.

9.7.7.5. Major Adverse Cardiovascular Events

The outcome for this analysis is definite and probable incident MACE (Section 9.3.2.6). Because of the potential cardioprotective effect of methotrexate (Marks and Edwards 2012), comparisons for MACE will not include the NBSM cohort.

In addition to the descriptive statistics and crude rates described in Section 9.7.7, analyses for MACE will include:

- Distribution of time to first MACE for the non-IL-17A biologic cohort and the ixekizumab cohort (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients)
- Crude rate, per 100 patient-years, of first MACE, as a component outcome and by individual event, for the non-IL-17A biologic cohort and the ixekizumab cohort (all patients, propensity trimmed populations and propensity matched populations, and unmatched patients); within cohorts, stratified by concomitant DMARD use

Any patient (and their associated follow-up time) with a physician-reported MACE without adequate supporting documentation for undergoing adjudication will be excluded from all

analyses of MACE. Propensity scores methods will be used as described in Section 9.7.4. Cox proportional hazards regression will be used to compare the rate of MACE between the ixekizumab and non-IL-17 biologic cohorts. All models will include the exposure cohort, concomitant NBSM use, and any variables that remain unbalanced after propensity score methods are applied (Table 3), and a time-dependent variable capturing concomitant psoriasis treatment. In the sensitivity analysis using matched cohorts, a sandwich variance estimator will be used to account for the matched data and methods used to account for within-patient correlation will be examined. Exposure will be censored at end of the study period, 90 days following discontinuation of a medication or switching to a new medication, at withdrawal from the registry, MACE, or death.

Proportional hazards of the exposure groups will be evaluated using Kaplan-Meier survival curves. If the proportional hazards assumption is violated, other models that relax the proportional hazards assumption will be considered.

9.7.7.6. Serious Hypersensitivity Reactions

The rate of serious hypersensitivity reactions (Section 9.3.2.7) in the psoriasis population is unknown. By its very nature, hypersensitivity is neither predictable nor preventable. The majority of hypersensitivity reactions observed during treatment with ixekizumab have been of a nonserious nature and of mild-to-moderate severity. The potential impact of the risk of hypersensitivity on public health is considered very low. The analysis of serious hypersensitivity reactions will include baseline characteristics for each exposure cohort and the crude rate, per 100 patient-years, will be calculated overall, and for each exposure cohort. The number of re-challenges after an event will be tabulated, as well as the number and rate of events occurring after a re-challenge. The descriptive analyses will be performed even if there is not a sufficient number of events to perform comparative analyses.

A comparative analysis will be undertaken to examine the risk of serious hypersensitivity reactions among patients treated with ixekizumab relative to patients in the non-IL-17 biologic cohort. The NBSM group will not be considered because of possible confounding; for example, the ability of methotrexate to prevent the activation of T cells and down regulation of B cells, thus reducing the risk of serious hypersensitivity reactions (Farhangian and Feldman 2015). An examination of concomitant NBSM treatment will be performed to determine if patients with concomitant NBSM use should be excluded. Any patient (and their associated follow-up time) with a physician-reported serious hypersensitivity reaction without adequate supporting documentation for undergoing adjudication will be excluded from all analyses of serious hypersensitivity reactions. Propensity score methods will be used as described in Section 9.7.4. Cox proportional hazards regression will be used to compare the rate of first serious hypersensitivity event between the ixekizumab and non-IL-17 biologic cohorts. All models will include the exposure cohort, concomitant NBSM use, and any variables that remain unbalanced after propensity score methods are applied (Table 3), and a time-dependent variable capturing concomitant psoriasis treatment. In the sensitivity analysis using matched cohorts, a sandwich variance estimator will be used to account for the matched data and methods used to account for within-patient correlation will be examined. Exposure time will be censored at the end of the

study period, 90 days following discontinuation of a medication or switching to a medication in an alternate exposure cohort, at withdrawal from the registry, first serious hypersensitivity event, or death.

Proportional hazards of the exposure groups will be evaluated using Kaplan-Meier survival curves. If the proportional hazards assumption is violated, other models that relax the proportional hazards assumption will be considered.

9.7.7.7. Demyelinating Disease

Demyelinating diseases (Section 9.3.2.8) are rare. Multiple sclerosis, the most common demyelinating disease, affects approximately 400,000 people in the United States (Tullman 2013). Although the incidence of demyelinating disease among patients with psoriasis is not published, estimates from other populations with autoimmune disease are quite low: 0.065 per 100 patient-years among patients with rheumatic disease exposed to tumour necrosis factor alpha (TNF-α) inhibitors (Fernández-Espartero et al. 2011); 0.075 per 100 patient-years among IBD patients exposed to TNF inhibitors; and 0.033 per 100 patient-years among IBD patients not treated with TNF inhibitors (Andersen et al. 2015). Although the registry is not expected to achieve adequate power to detect reasonable relative risks for demyelinating disease, an exploratory comparative analysis will be undertaken to compare the risk among patients in the ixekizumab cohort relative to patients in the NBSM and non-IL-17 biologic cohorts. The descriptive analyses will be performed even if there is not a sufficient number of events to perform comparative analyses. Any patient (and their associated follow-up time) with a physician-reported demyelinating disease without adequate supporting documentation for undergoing adjudication will be excluded from all analyses of demyelinating disease.

The analysis of demyelinating disease will include baseline characteristics for each exposure cohort and the crude rate, per 100 patient-years, overall, and for each exposure cohort. Propensity score methods will be used as described in Section 9.7.4. Cox proportional hazards regression will be used to compare the rate of demyelinating events between the ixekizumab and non-IL-17 biologic cohorts. All models will include the exposure cohort, concomitant NBSM use, and any variables that remain unbalanced after propensity score methods are applied (Table 3), and a time-dependent variable capturing concomitant psoriasis treatment. In the sensitivity analysis using matched cohorts, a sandwich variance estimator will be used to account for the matched data and methods used to account for within-patient correlation will be examined. Exposure time will be censored at the end of the study period, 90 days following discontinuation of a medication or switching to a medication, at withdrawal from the registry, a demyelinating event, or death.

Proportional hazards of the exposure groups will be evaluated using Kaplan-Meier survival curves. If the proportional hazards assumption is violated, other models that relax the proportional hazards assumption will be considered.

9.7.7.8. Gastrointestinal Perforation

The incidence of gastrointestinal perforations (Section 9.3.2.9) is not well characterized within the psoriasis population. If the incidence of gastrointestinal perforation within the psoriasis

registry population is rare, this study will not likely achieve adequate power to detect a reasonable relative difference in the risk among ixekizumab-exposed patients relative to the other exposure groups. Although the registry may not achieve adequate power to detect reasonable relative risks for gastrointestinal perforations, an exploratory comparative analysis will be undertaken to compare the risk among patients in the ixekizumab cohort relative to patients in the NBSM and non-IL-17 biologic cohorts. The analysis will include baseline characteristics for each exposure cohort and the crude rate, per 100 patient-years, overall, for each exposure cohort. Propensity scores will be used as described in Section 9.7.4. Cox proportional hazards regression will be used to compare the rate of demyelinating events between the ixekizumab and non-IL-17 biologic cohorts. All models will include the exposure cohort, concomitant NBSM use, and any variables that remain unbalanced after propensity score methods are applied (Table 3), and a time-dependent variable capturing concomitant psoriasis treatment. In the sensitivity analysis using matched cohorts, a sandwich variance estimator will be used to account for the matched data and methods used to account for within-patient correlation will be examined. Exposure time will be censored at the end of the study period, 90 days following discontinuation of a medication or switching to a new medication, at withdrawal from the registry, gastrointestinal perforation, or death. The descriptive analyses will be performed even if there is not a sufficient number of events to perform comparative analyses. Any patient (and their associated follow-up time) with a physician-reported gastrointestinal perforation without adequate supporting documentation for undergoing adjudication will be excluded from all analyses of gastrointestinal perforation. Proportional hazards of the exposure groups will be evaluated using Kaplan-Meier survival curves. If the proportional hazards assumption is violated, other models that relax the proportional hazards assumption will be considered.

9.7.7.9. Patient Subgroups of Special Interest

The Corrona Psoriasis Registry will be used to monitor the incidence and nature of protocol defined AEs among the very elderly (≥75 years). Baseline characteristics will be described for enrolled patients aged 75 or older. The incidence rate of protocol defined AEs will also be provided for this subgroup of special interest.

9.7.8. Sensitivity Analysis

As a sensitivity analysis to the primary analysis considering only adjudicated events, the main descriptive analyses (crude and age- and gender-standardized) incidence rates and comparative (Cox proportional hazard model comparing time-to-first event between cohorts in a propensity score trimmed population) will be performed for each outcome on all physician-reported events.

Propensity score matching, as described in Section 9.7.4, will be completed as a sensitivity analysis to the primary approach of propensity score trimming for common support.

Several sensitivity analyses will be performed to examine the impact of assumptions on study conclusions. An underlying assumption for all of the analyses presented in this protocol is the absence of unmeasured confounding. It is possible that all potential confounding variables may not be available within the Corrona Psoriasis Registry. To address this issue, a rule out approach, as presented by Delaney and Seeger (2013) will be used for primary and secondary

comparative analyses to quantify the effect that an unmeasured confounder would have on study results.

Additional sensitivity analyses are presented, by outcome, below.

9.7.8.1. Malignancy

9.7.8.1.1. Analysis of All Physician-Reported Events

As a sensitivity analysis to the primary analysis considering only events adjudicated as probable or definite, the main descriptive analyses (crude and age- and gender-standardized) incidence rates and comparative (Cox proportional hazard model comparing time-to-first event between cohorts in a propensity score trimmed population) will be performed for each outcome on all physician-reported events (reported on an MD form or a TAE form and regardless of availability of supporting documentation).

9.7.8.1.2. Propensity Score Matched Analysis

Several sensitivity analyses will be performed to examine the impact of analysis decisions and assumptions on the study conclusions. The main sensitivity analysis to be performed is that of a propensity score matched analysis. In this analysis, exposure episodes will be matched within calendar-specific time periods. In the comparative analyses, a sandwich variance estimator will be used to account for the matched observations.

9.7.8.1.3. Hierarchical Exposure Cohort Assignment

For the primary endpoint, malignancy and the secondary outcome of NMSC, a hierarchical assignment of exposure cohort was performed which conservatively assigned events to the ixekizumab cohort once ixekizumab exposure had occurred, even if later NBSM or non-IL-17 biologic exposure occurred. In this assignment, the hierarchy of assignment was ixekizumab > non-IL-17 biologic > NBSM. To evaluate the effect of this analytic decision, a sensitivity analysis which switches the hierarchical assignment of exposure cohort and performs the descriptive and comparative analyses, switching the hierarchy of assignment to non-IL-17 biologic > ixekizumab > NBSM. In this assignment, once non-IL-17 biologic exposure occurs, events are assigned to the non-IL17 exposure cohort even if subsequent ixekizumab exposure occurs.

9.7.8.1.4. Assessment of the Risk of Malignancies for Biologic versus Nonbiologic Systemic Medications

NBSM users are expected to be a small proportion of the Corrona Psoriasis Registry population. Comparisons with this group of patients will be made to obtain information about the potential risk of malignancy, excluding NMSC, associated with ixekizumab that may not be found with a comparison to other biologic medications; however, these analyses will be exploratory given the small number of NBSM users expected in the registry. If the exploratory analysis comparing ixekizumab to the NBSM group identifies a potential increased risk of malignancy, excluding NMSC, associated with ixekizumab, an additional exploratory analysis comparing the non-IL-17 biologic medication cohort to the NBSM cohort will be conducted as a means of evaluating

whether the potential risk observed with ixekizumab is similar to the risk observed with other biologic medications.

9.7.8.1.5. Assessment of the Risk of Malignancies between Durations of Ixekizumab Exposure

This sensitivity analysis will consider the risk of malignancy, excluding NMSC, associated with cumulative duration of ixekizumab exposure, and will be conducted regardless of results from primary analysis. Only patients with ixekizumab exposure initiated at or after registry enrolment will be included in this analysis, unless the sample size is prohibitively small. Cumulative duration of ixekizumab exposure will be captured from physician enrolment or follow-up forms and will be calculated for each person in the ixekizumab cohort. Exposure time will commence upon ixekizumab initiation and will continue until the drug discontinuation date, initiation of another IL-17 inhibitor, the development of a malignancy, death, withdrawal from the study, or end of study follow-up period. Analyses will include crude rates of malignancies, excluding NMSC, among quintiles of ixekizumab exposure. Additionally, a logistic regression will be performed to assess the association of duration of ixekizumab exposure with malignancy, excluding NMSC. The model will include duration of exposure and important confounding variables (Table 3). This analysis may be modified to focus on the class of IL-17 inhibitors rather than ixekizumab if capturing ever exposure to ixekizumab without other IL-17 inhibitor use is infeasible.

9.7.8.1.6. Assessment of the Risk of Malignancy among all IL-17A Inhibitors versus non-IL-17A Biologics

If the primary analysis reveals a significant result, either in favour of ixekizumab or the comparator, a sensitivity analysis that considers the IL-17A inhibitors (ixekizumab and secukinumab) as a class will be performed. Exposure cohorts will be constructed as described in Section 9.3.1.1 and analysis will proceed as outlined in Section 9.7.6.

9.7.8.1.7. Assessment of the Risk of Malignancy among non-IL-17A Biologics

If the primary analysis reveals a significant result, either in favour of ixekizumab or the comparator, a sensitivity analysis in which one of the non-IL-17 biologics will be identified on its own compared to the remaining non-IL-17 biologics will be performed. Exposure cohorts will be constructed as described in Section 9.3.1.1 and analysis will proceed as outlined in Section 9.7.6.

9.7.8.1.8. Assessment of Different Latency Periods for Malignancy

Given the latency period for malignancy detection, malignancies detected shortly after initiation of a drug are likely malignancies that were present but not detectable prior to the initiation, and therefore not due to the newly initiated drug. To account for this latency period, a sensitivity analysis will be conducted in which the exposure period in the malignancy cohorts will begin 6 months after drug initiation. If the initiation beginning the exposure period is the first while on the registry, the first 6 months after initiation will not be included in any exposure cohort. If the initiation of ixekizumab beginning the exposure period occurs after exposure to comparator drug,

the first 6 months after initiation will be included in the exposure cohort of the comparator. Only exposure episodes for medication initiations at or after enrollment will be considered for the analysis. Incidence rates and hazard ratios comparing risk between cohorts will be performed in the propensity score trimmed population. The analyses will be repeated using a 12-month window to evaluate a longer latency. All analyses will proceed as described in Section 9.7.6.

9.7.8.1.9. Assessment of Detection Bias

If the primary analysis reveals a significant result, in favour of either ixekizumab or the comparator, a sensitivity analysis will be conducted that examines the incidence rate and hazard ratios comparing risk between cohorts during several periods of time following initiation. Specifically, due to an increase in monitoring immediately following initiation of a drug, the incidence rate may appear highest immediately following drug initiation, decline in the time period following the initial intensified monitoring time, and stabilize for the time periods further from initiation. To explore whether this pattern exists and whether it differs by cohort, we will examine incidence rates and hazard ratios comparing medication cohorts in several time periods following initiation: 0 to 6 months, >6 months to 1 year, >1 year to 2 years, >2 years to 4 years, and >4 years. To examine incidence rates within these time periods, exposure cohorts will be created that begin at the start of the time period and end at the end of the time period. Any events that fall outside of the time period will not be included in the incidence rate calculations. The time periods examined may depend on the frequency of events experienced in different time periods. Only exposure episodes for medication initiations at or after enrollment will be considered for the analysis.

9.7.8.2. NMSC

If the secondary analysis reveals a significant result, either in favour of ixekizumab or the comparator, a sensitivity analysis that considers the IL-17A inhibitors (ixekizumab and secukinumab) as a class will be performed. In addition, a sensitivity analysis in which one of the non-IL-17 biologics will be identified on its own compared to the remaining non-IL-17 biologics will be performed. Exposure cohorts will be constructed as described in Section 9.3.1.1 and analysis will proceed as outlined in Section 9.7.6.

9.7.8.3. Secondary Outcomes, Excluding NMSC

An analysis in which a 30-day risk window will be used instead of a 90-day risk window will be completed as a sensitivity analysis. When there is an overlap of the risk period of a drug stopping (plus 30 days) and a new drug starting (the start begins in the 30-day window), the risk period of the overlap is assigned to the starting drug.

9.7.8.4. Serious Infections

An analysis that considers all serious infections (that is, including infections other than the first) will also be conducted as a sensitivity analysis. Propensity methods will be completed described in Section 9.7.4. Generalized estimating equation (GEE) negative binomial regression models with a log link will be used to estimate the relative rate and 95% CI for all serious infections between the ixekizumab and NBSM cohorts, and the ixekizumab and non-IL-17 biologic cohorts. The within-patient association will be accounted for by assuming a first-order auto-

regressive correlation structure. Any variables that remain unbalanced after propensity score methods are applied will be included in the model.

9.7.8.5. Opportunistic Infections

An analysis that includes all serious opportunistic infections will also be conducted as a sensitivity analysis. Propensity methods will be completed described in Section 9.7.4. Generalized estimating equation (GEE) negative binomial regression models with a log link will be used to estimate the relative rate and 95% CI for all opportunistic infections between the ixekizumab and NBSM cohorts, and the ixekizumab and non-IL-17 biologic cohorts. The within-patient association will be accounted for by assuming a first-order auto-regressive correlation structure. Any variables that remain unbalanced after propensity score methods are applied will be included in the model.

9.7.8.6. Inflammatory Bowel Disease

An analysis that includes all IBD flares in patients already diagnosed with IBD will also be conducted as a sensitivity analysis. Propensity methods will be completed described in Section 9.7.4. GEE negative binomial regression models with a log link will be used to estimate the rate and 95% CI for IBD flares. The within patient association will be accounted for by assuming a first-order auto-regressive correlation structure. All models will include the exposure cohort, concomitant NBSM use, concomitant non-ixekizumab biologic use, and concomitant ixekizumab- use (as defined in Section 9.3.1.2). Any variables that remain unbalanced after propensity score methods are applied may also be included in the model.

9.8. Quality Control

Refer to the current version of the Corrona Psoriasis Registry Protocol for details.

9.9. Limitations of the Research Methods

The current study uses data collected by the Corrona Psoriasis Registry, the first US psoriasis registry co-developed and co-administered by a not-for-profit agency. Data for the registry are systematically collected from patients and physicians and are independently analysed by Corrona statisticians. The Corrona Psoriasis Registry is expected to be the largest, single source of systemically collected longitudinal data on the safety of ixekizumab in routine clinical practice. Exposure, outcome, and covariate information is collected by physician and patient reports. Supporting documentation is requested for all TAEs for review by an independent adjudication committee, thereby limiting the possibility of information bias. In addition to the robust data collection, this study uses multiple methodologies, including propensity scores, to assess the association of AEs. Even with these strengths, it will be important to consider the study results in light of the following limitations.

9.9.1. New Users versus Continuing Users

The Corrona Psoriasis Registry enrols patients who have initiated an FDA-approved systemic psoriasis treatment within the previous 12 months (Figure 2). As a result, new enrolees to the registry may be either a new user or continuing user. Time at risk for new users begins at the

start of drug exposure (similar to time at risk for those starting a medication after registry enrolment) whereas for patients enrolling in the registry continuing a previously initiated medication, time at risk for the current study begins at registry enrolment. However, these patients (continuing users) are a select group of patients who have "survived" from the time of drug initiation to registry enrolment. Consequently, they typically have greater drug tolerability and are less likely to experience an AE than new users. Even if all pre-enrolment exposure time is excluded from the analysis (as is planned), including follow-up time for medications initiated prior to registry enrolment has the potential to bias the estimates towards the null. Adjusting for baseline confounders is also more complicated, as the baseline time is different for new and continuing users. To address these issues, separate propensity score models will be estimated for medication initiations that occurred prior to registry enrolment and medication initiations occurring at or after registry enrolment in the primary analysis of malignancy. Propensity score trimming and matching will also happen separately between the groups. The analyses of secondary, non-malignancy outcomes excludes all registry follow-up time for medication initiated prior to registry enrolment, so separate analyses will not be performed for secondary analyses examining non-malignancy outcomes.

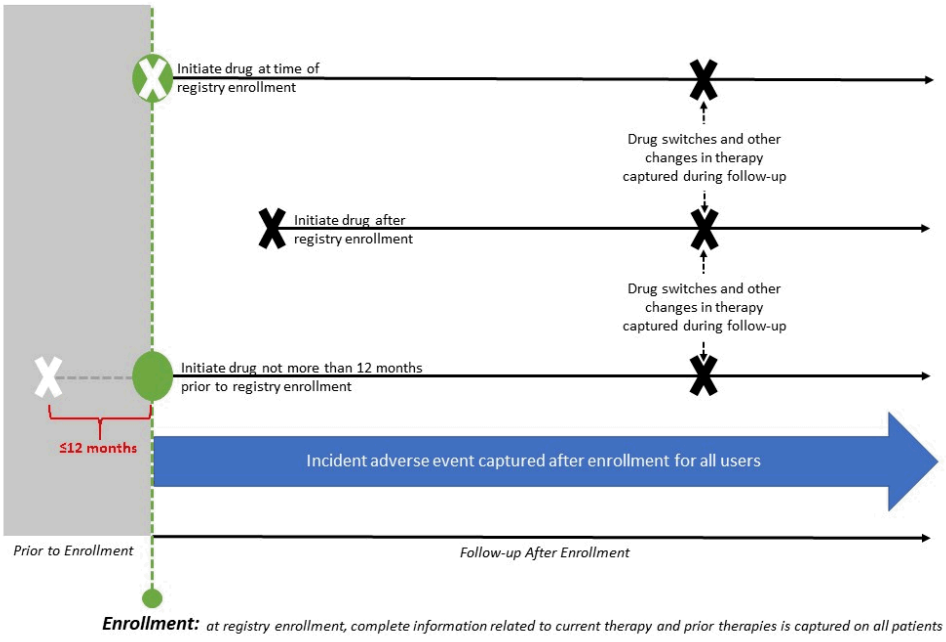

Figure 2. Registry enrolment and follow-up time.

9.9.2. Channelling Bias in Observational Studies

Drug exposure in pharmacoepidemiological studies does not occur at random and is a result of patient, physician, and system-related factors. When these factors are associated with the outcome of interest, comparisons of different drug exposure cohorts will be confounded because of channelling bias. The current study addresses this limitation by applying propensity score matching, as appropriate for each outcome. Propensity scores address this imbalance by

providing a mechanism to compare patients with concordant baseline risk but discordant exposure (Schneeweiss 2007). Calendar specific propensity score methods will be implemented to account for changes in treatment patterns that commonly occur after a new drug enters the marketplace; however, propensity scores are only able to adjust for measured confounders. The possibility of unmeasured confounding and the possible influence on study results will be considered in the final report.

9.9.3. Assessing Malignancy Risk in a Real-World Setting

Malignancy outcomes require a long developmental period, and as a result, are not easily attributed to a particular drug exposure. To account for this ambiguity, the primary analysis considers the risk of malignancy excluding NMSC associated with the use of ixekizumab, regardless of subsequent medication changes. Although this approach is considered conservative from the standpoint that attribution of a malignancy to ixekizumab will not be missed, it ignores the duration of ixekizumab exposure and exposure to other systemic medications.

Typically, the risk of malignancy increases with increasing exposure to an identified risk factor. If ixekizumab were a risk factor for malignancy, combining patients with varying durations of exposure has the potential to bias the measure of association towards the null. To address this issue, an analysis that examines the duration of ixekizumab use will be performed.

Another challenge of studying malignancy is the effect of screening on the incidence rate. If the primary analysis reveals an association between exposure to ixekizumab and malignancy, or exposure to an IL-17 inhibitor and malignancy, a sensitivity analysis will be conducted that eliminates malignancy cases within the first 6 months of follow-up, because of the low likelihood of biologic plausibility and the possibility of detection bias. Only new initiators at baseline will be considered for the analysis, in order to identify malignancy cases that occur within 6 months of drug initiation.

Finally, the class of IL-17 inhibitor biologics is fairly new, and questions remain regarding the risk of ixekizumab relative to other IL-17 medications. If the primary analysis is able to consider the risk of malignancy associated with ixekizumab, rather than the class of IL-17 inhibitors, a sensitivity analysis that compares ixekizumab to other IL-17 inhibitors will be conducted. This sensitivity analysis will test the hypothesis that the effects of ixekizumab and other IL-17 inhibitors on the incidence of malignancy are similar.

9.9.4. Assessing Loss to Follow-Up, Adverse Events, and Death

During the course of the observational period, it is expected that some patients will be lost to follow-up. The Corrona Psoriasis Registry requires that multiple follow-up attempts are made before a patient is considered lost. Physicians are required to document all follow-up attempts and submit an exit questionnaire before a patient is disenrolled from the registry.

It is also possible that a TAE or death may occur during the course of follow-up without the investigator's knowledge. Corrona implements a systematic and comprehensive AE reporting system as well as linkage to the National Death Index to identify deaths and collect data on date and cause of death. Although these efforts cannot completely eliminate the possibility that an

outcome will be missed, any failed report is expected to occur at random and should not be associated with exposure status.

9.9.5. Generalizability

The Corrona Psoriasis Registry includes a sample of adults with psoriasis who are not necessarily representative of all adults with psoriasis in the United States. In particular, these are patients with psoriasis with clinical physician visits. Patients are recruited by the physician who is required to indicate a diagnosis upon enrolment of the patient into the Corrona Psoriasis Registry. Comparison of baseline characteristics with other data sources containing patients with psoriasis (insurance databases, for example), may help to clarify the extent to which results from the registry have external validity. Regardless, findings from this study are expected to have internal validity and provide valuable information about the long-term safety of ixekizumab.

9.9.6. Capture of Concurrent (Non-psoriasis) Medications

The Corrona Psoriasis Registry includes detailed data capture on a range of patient, clinical, and disease-related characteristics in addition to detailed capture of events occurring in the registry population. Full capture of all exposed concurrent medications (prior to enrolment and during registry participation) *not used for the treatment of psoriasis* is limited in the context of this observational registry, to balance critical data collection points with data collection burden for participating patients and their dermatologists. For this reason, covariates being selected for adjusted analyses are limited to those non-psoriasis medications that are captured uniformly across registry participants (vs. those who may experience a TAE during registry participation). As a result, effect modification of GI perforation by glucocorticoid use, and possible alternative explanations of serious infections and serious hypersensitivity reactions, cannot be assessed.

9.10. Other Aspects

Not applicable.

10. Protection of Human Subjects

The Corrona-sponsored non-interventional, observational study protocol is subject to central institutional review board (IRB) approval and regulations as required by US law. Participating investigators must also obtain IRB approval prior to initiating primary data collection procedures. Sponsor and investigator progress reports are submitted to the IRB in compliance with noninterventional study regulations. The I1F-MC-RHBT protocol does not require additional IRB approval or consent.

11. Management and Reporting of Adverse Events/Adverse Reactions

Adverse Events

The investigator or other study personnel will collect via an electronic case report form (CRF) any protocol-defined AEs, including all associated fatal outcomes, occurring in temporal association with Lilly product(s) that are under evaluation as defined in this protocol and defined in Section 9.3.2. All other AEs will not be actively collected because of lack of relevance to the study outcomes.

Investigators and other study personnel are requested to report any serious adverse reactions (SARs) with Lilly products not under evaluation in this protocol or SARs with non-Lilly products to the appropriate party (for example, regulators or the marketing authorization holder) as they would in normal practice as required by applicable laws, regulations, and practices.

Investigators and other study personnel are not obligated to actively collect AEs or serious AEs (SAEs) in patients once they have discontinued from the study. However, if the investigator learns of any SAE, including death, at any time after the patient has discontinued from the study, and the event is considered reasonably possibly related to the Lilly product under evaluation, the investigator must promptly notify Lilly.

Protocol Defined Adverse Event Reporting Timing for Primary Data Collection Only

All Corrona investigators will report any protocol-defined SAE arising in temporal association with the Lilly product under evaluation to Corrona within 24 hours of awareness of the event. Corrona will then report the event to Lilly within 72 hours via secure email. The reports issued via telephone are to be immediately followed with official notification on study-specific SAE forms. A protocol defined SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- or is considered significant by the investigator for any other reason, such as important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events (ADEs) when, based upon appropriate medical judgement.

When a condition related to the ixekizumab single-dose prefilled autoinjector or single-dose prefilled syringe necessitates medical or surgical intervention to preclude permanent impairment

of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

The investigator or other study personnel will record any **nonserious** protocol-defined AE arising in temporal association with the Lilly products under evaluation within 30 days of awareness of the event via electronic CRF.

Product Complaints

Lilly collects product complaints on investigational products and drug delivery systems used in medical research studies in order to ensure the safety of study patients, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded comparator drugs or concomitant drug/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

Investigators or other study personnel are instructed to report product complaints as they would for products in the marketplace.

12. Plans for Disseminating and Communicating Study Results

Interim and final reports will be submitted to regulatory agencies. The study will also be registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Registry, and the study findings will be submitted to a scientific congress and submitted to a peer-reviewed journal.

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Annex 1. List of Standalone Documents

The following can be provided on request:

Number	Document Reference No.	Date	Title
1.	Not applicable	22 September 2015	Corrona Psoriasis Registry Protocol*
2.	Not applicable	22 April 2019	Corrona Psoriasis Registry: Minimum Supporting Documents by Event Type (reference table)

*Updates can be provided upon request

Annex 2. ENCePP Checklist for Study Protocols

Study title: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (may include psoriatic arthritis) in the Course of Routine Clinical Care

Study reference number: EUPAS18132

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

Comments:

[1] 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.
[2] Date from which the analytical dataset is completely available.

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)	☒	☐	☐	9.9.5
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	9.7.6
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary, or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measure of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7.6 & 9.7.7
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm [NNH] per year)	☒	☐	☐	9.7.6 & 9.7.7

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
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?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	7
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	7
4.2.4 Disease/indication?	☒	☐	☐	9.1
4.2.5 Duration of follow-up?	☒	☐	☐	9.2.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

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)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.1.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1.2

Comments:

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?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2.1-9.3.2.9
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.2.1-9.3.2.9

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYs, health care services utilisation, burden of disease, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7.2-9.7.7
7.1.1 Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7.2-9.7.5
7.2 Does the protocol address:				
7.2.1 Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9.5
7.2.2 Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.7.3
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.3.3 & 9.4

Comments:

Section 8: Effect 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)	☒	☐	☐	9.7.5

Comments:

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)	☒	☐	☐	9.3.1.1 & 9.3.1.2
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2.1-9.3.2.9
9.1.3 Covariates?	☒	☐	☐	9.3.3
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)	☒	☐	☐	9.3.1.1 & 9.3.1.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2.1-9.3.2.9
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical [ATC] Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.6 & 9.7.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.6 & 9.7.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7.1
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.2-9.7.7
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.6.1.1
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

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)	☒	☐	☐	9.4
11.2 Are methods of quality assurance described?	☒	☐	☐	9.4

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Data storage and quality assurance is handled by the Corrona Psoriasis Registry. The current protocol references the Corrona Psoriasis Registry Protocol.

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 biases?	☒	☐	☐	
12.1.2 Information biases?	☒	☐	☐	
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- 9.9.5
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.3.1&9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	10

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.4

Comments:

Data storage and protection is handled by the Corrona Psoriasis Registry. The current protocol references the Corrona Psoriasis Registry Protocol.

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

Comments:

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: 21-JUN-2019

Signature: PPD

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