Protocol I1F-MC-B015
Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Paediatric Psoriasis

Protocol Electronically Signed and Approved by Lilly: approval date provided below

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Post-authorisation Safety Study (PASS) Information

Title	Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Paediatric Psoriasis
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Research question and objectives	The objectives of this study are to monitor the uptake of ixekizumab in a real-world paediatric psoriasis population, to characterise the demographic and clinical characteristics of paediatric patients receiving ixekizumab and appropriate comparator medications, and to obtain information about the long-term safety pertaining to serious infections and inflammatory bowel disease. Once target study size is reached, an additional objective is to compare the incidence of serious infections and IBD in children exposed to ixekizumab to: (1) Children with plaque psoriasis who were treated with another biologic approved for paediatric use (2) Children with plaque psoriasis who were treated with systemic non-biologic treatments (3) Children with plaque psoriasis who were treated only with non-systemic treatments. The null hypothesis is that incidence of SI and IBD are similar in paediatric psoriasis patients exposed to ixekizumab when compared to paediatric populations unexposed to ixekizumab.
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1. List of Abbreviations

Term	Definition
AE	Adverse event
CD	Crohn's disease
CI	Confidence interval
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	Ethical review board
EU PAS	European Union Post-authorisation Studies
FDA	Food and Drug Administration
GPI	Generic Product Identifier
HCPCS	Healthcare Common Procedure Coding System
HIRD	HealthCore Integrated Research Database
IBD	Inflammatory bowel disease
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
IR	Incidence rate
IRR	Incidence rate ratio
MRP	Medical Record Plan
NDC	National Drug Code
PASS	Post-authorisation safety study
PS	Propensity score
PHI	Protected health information

PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
SAP	Statistical analysis plan
SI	Serious infection
UC	Ulcerative colitis
US	United States

3. Responsible Parties

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4. Abstract

Title
Observational Post-Marketing Safety Study of Ixekizumab for the Treatment of Paediatric Psoriasis
Version: 1.0
Main Author: PPD

Rationale and background:

Ixekizumab is a humanised IgG4 monoclonal antibody that binds with the IL-17A cytokine. The paediatric dosage is administered once monthly as a subcutaneous injection, depending on the child's weight. Ixekizumab received approval from the Food and Drug Administration (FDA) in March of 2020 and the EMA in June 2020 for paediatric patients aged 6 to less than 18 years of age with moderate-to-severe plaque psoriasis who are candidates for systemic treatment and phototherapy. The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has requested a new study to evaluate the long-term safety study of ixekizumab in paediatric patients with psoriasis.

Research question and objectives

The objectives of this study are to monitor the exposure to ixekizumab among children 6 to less than 18 years of age with plaque psoriasis and to measure the incidence of serious infections (SI) and flares of both new onset and prevalent inflammatory bowel disease (IBD) (Crohn's disease (CD) and ulcerative colitis (UC)) among children exposed to ixekizumab. Once target study size is reached, an additional objective is to compare the incidence of serious infections and IBD in children exposed to ixekizumab to children with plaque psoriasis who were treated with (1) another biologic approved for paediatric use and (2) systemic non-biologic treatments and (3) only non-systemic treatments.

The null hypothesis is that incidence of SI and IBD are similar in paediatric psoriasis patients exposed to ixekizumab when compared to paediatric populations unexposed to ixekizumab.

Study design

We are proposing a two-phased approach where Phase 1 includes product uptake monitoring to achieve sufficient patient accrual. Once the target number of patients are accrued during Phase 1, Phase 2 will include a cohort study with comparative analyses of the incidence of safety outcomes among children with plaque psoriasis who have exposure to ixekizumab relative to three comparator groups.

Population

This study will include children newly exposed to ixekizumab or comparator medications as identified through pharmacy and medical claims in the HealthCore Integrated Research Database (HIRD). The three comparator groups are (1) children 6-<18 years of age treated with etanercept, which is approved for paediatric patients with moderate-to-severe plaque psoriasis; (2) children 6-<18 years of age who were treated with systemic non-biologic medications such as acitretin, cyclosporine, and methotrexate; (3) children 6-<18 years of age treated only with non-systemic treatments such as topical corticosteroids and calcipotriene.

Across the cohorts, children will be required to have a minimum of six months baseline eligibility prior to a dispensing of the study drug.

Variables

In Phase 1, exposure to ixekizumab or comparators will be ascertained from claims based on the National Drug Code (NDC) or Generic Product Identifier (GPI) for outpatient pharmacy dispensing and Healthcare Common Procedure Coding System (HCPCS) codes for infusions that occur in a healthcare setting. Defining exposure episodes for the primary and sensitivity analyses will depend on use of these medications in routine clinical practice. Therefore, preliminary work evaluating drug utilisation will be conducted before finalising exposure episodes. Outcomes and covariates, including demographics, clinical characteristics, healthcare utilisation, and medication use will be ascertained using administrative claims. Additionally, in Phase 1, outcomes will be validated by medical record review.

Data sources

This study will be conducted using the HIRD, a longitudinal medical and pharmacy claims database from health plan members across the United States (US). Depending on accrual of exposed children, additional data sources may be added during Phase 1 (uptake monitoring). All available data prior to the dispensing of ixekizumab or comparators will be used to assess baseline characteristics. Claims will be utilised as the data source for exposure status, endpoints, and covariates. Medical records will be utilised to validate endpoints as necessary.

Study size

The available number of exposed children will depend on the uptake of ixekizumab in the US among children between the ages of 6 to <18. With 392 ixekizumab-treated children and 392 etanercept-treated children, the study will achieve 80% power to detect a 16.8-fold difference in the incidence of SI and a 3.9-fold difference in the incidence in new onset or exacerbations of IBD between ixekizumab and etanercept. Additionally, with 2,352 children prescribed systemic non-biologic treatments and 3,528 children prescribed only non-systemic treatments, the study will achieve 80% power with to detect at least an 8.9-fold difference in the incidence of SI and IBD between ixekizumab and systemic non-biologic treatment or non-systemic treatment. If we are not on track to accrue the targeted number of patients for an interim analysis by second quarter of 2023, we will reach out to additional data sources to determine the number of ixekizumab-exposed children that could be identified by expanding the study to include multiple databases, or consider extending the timeline of the study. Feasibility of continuing the study, either as a single database or a multi-database study, will be considered in consultation with regulatory authorities.

Data analysis

- In Phase 1, the number of children exposed to ixekizumab or comparator medications, duration of exposure, and total outcomes will be identified and validated.

- In Phase 2, we will describe children who were exposed either to ixekizumab, a biologic comparator (etanercept), non-biologic comparator, or only non-systemic comparators, with respect to demographic, clinical, treatment, and utilisation characteristics.

- We will use exposure propensity scores to match comparators to the ixekizumab cohort. Covariate balance will be assessed using absolute standardised differences with a target value of less than 0.1 [1].

- For each outcome, the incidence of SI and flares of existing or new IBD will be presented for each exposure group. Incidence rate ratios (IRR) and their corresponding 95% confidence intervals (CI) will be calculated comparing ixekizumab-exposed children to children exposed to etanercept, non-biologic medications, and non-systemic medications. Effect estimates will be stratified by duration of exposure, age, and gender.

Milestones

Upon approval of the protocol and statistical analysis plan (SAP), data collection will begin by 31 August 2021 using data that spans from March of 2020 through October 2025. Annual product uptake monitoring in Phase 1 will monitor ixekizumab and comparator drug uptake to determine feasibility and optimal timing for initiation of cohort surveillance (Phase 2). Uptake monitoring may suggest the need to incorporate additional data sources, extend the time period for uptake monitoring, or both. The Final Study Report is expected to be completed by 30 April 2026.

5. Amendments and Updates

Not applicable at this time.

6. Milestones

Milestone	Planned date
Start of data collection	31 August 2021
Interim report of study results	30 June 2023[a]
End of data collection	30 October 2025
Final report of study results	30 April 2026

[a] Interim analysis will be performed once one-third of targeted ixekizumab exposures have accrued. If a sufficient number of exposures have not accrued for an interim analysis by June 2023, we will reach out to additional data sources to determine the number of ixekizumab-exposed children that could be identified by expanding the study to include multiple databases. Feasibility of continuing the study, either as a single database or a multi-database study, will be considered in consultation with regulatory authorities.

7. Rationale and Background

Psoriasis is a systemic autoimmune condition affected by genetic and environmental factors [2]. Approximately 30-50% of psoriasis patients develop psoriasis before the age of 20. In Europe and North America, the prevalence of psoriasis among paediatric patients ranges between 1.3-2.1% with an estimated incidence rate of 40.8/100,000 person-years [3-5]. Several reports indicate that the incidence of paediatric psoriasis has been increasing over time from 29.6/100,000 person-years in 1974 to 62.7/100,000 person-years in 1995 [4, 6]. The median age of onset among paediatric psoriasis patients is between 7 and 10 years [4]. The hallmark of plaque psoriasis is plaques (patches) of inflamed, red skin covered with silvery scales. Approximately 80-90% of psoriasis patients have the plaque form of psoriasis, causing itching and pain, most typically involving skin of the scalp, trunk, buttocks, and limbs [7]. Psoriatic arthritis is one of the most common coexisting conditions, as about 30-40% of psoriasis cases also develop psoriatic arthritis [8, 9].

Paediatric onset psoriasis differs from its adult counterpart as pharyngitis, stress, and trauma are more common triggers of disease activity [4]. Upper respiratory infections appear to be the most common trigger for the onset of paediatric plaque psoriasis, but other environmental triggers such as trauma, drug exposure, and physical or psychological stress have been linked to paediatric onset also.

There are currently no international guidelines for the medical treatment of paediatric psoriasis, only published case reports and/or series. This has complicated the management of psoriasis systemic therapy among moderate-to-severe paediatric patients. Thus, most of the systemic treatments for paediatric psoriasis are off-label and based on established guidelines for adults with psoriasis [10]. The United States (US) based paediatric guidelines highlight the use of biologic medications indicated for other conditions as effective treatment for moderate-to-severe paediatric psoriasis [11]. Although earlier publications point to the primary goal in the treatment of childhood psoriasis as effective control of disease, more recent work suggests a more aggressive approach. Currently, etanercept, adalimumab, ustekinumab, and ixekizumab are the only biologics approved for use in the United States and the European Union for the moderate-to-severe paediatric psoriasis populations. Secukinumab has been approved for paediatric plaque psoriasis use in the EU but not in the US. Topical therapies or phototherapy are more widely used, but are likely not as effective in treating moderate-to-severe psoriasis among paediatric patients [10].

Ixekizumab is a humanised IgG4 monoclonal antibody that binds with the IL-17A cytokine. It is currently approved in the US and Europe for moderate-to-severe plaque psoriasis in paediatric patients aged 6 to less than 18 years of age. Ixekizumab is administered once monthly as a subcutaneous injection, with the paediatric dosage depending on the child's weight. Investigation concerning the effects of ixekizumab on moderate-to-severe paediatric plaque psoriasis is currently limited to one randomised, double-blind, placebo-controlled trial among children (N=182). Results demonstrate that ixekizumab improves both pathologic skin features and clinical symptoms of chronic moderate-to-severe plaque psoriasis. However, there is some concern that by blocking IL-17-mediated chemokine production, ixekizumab may increase susceptibility to infections [12]. Additional long-term safety studies are necessary to confirm these findings.

8. Research Question and Objectives

The objectives of this study are to monitor the uptake of ixekizumab in a real-world paediatric psoriasis population, to characterise the demographic and clinical characteristics of paediatric patients receiving ixekizumab and appropriate comparator medications, and to obtain information about the long-term safety pertaining to serious infections and inflammatory bowel disease.

The null hypothesis is that incidence of SI and IBD are similar in paediatric psoriasis patients exposed to ixekizumab compared to paediatric populations unexposed to ixekizumab.

9. Research Methods

9.1. Study design

This cohort study uses US administrative health care data from the HealthCore Integrated Research Database (HIRD). It will take place in two phases as described below.

9.2. Phase 1: Uptake Monitoring

During the uptake monitoring phase, children between the ages of 6 to less than 18 with exposure to ixekizumab or appropriate comparator medications will be identified and characterised with respect to demographics and clinical characteristics. Surveillance for serious infections (SI) and inflammatory bowel disease (IBD) will be performed, and measures of disease occurrence (numbers, percentages, and incidence rates) will be presented in annual reports. These outcomes will be validated via medical record review for the interim and final study reports.

Uptake monitoring is expected to continue for the duration of the study to ensure identification of ixekizumab-exposed patients. The results of this phase of the study will determine the feasibility for initiation of a comparative analysis (Phase 2) and determine the need to include additional data sources, extend the study timeline, or both (see Section 9.8).

9.3. Phase 2: Comparative Safety Analysis

The purpose of Phase 2 is to conduct comparative analyses to assess the association between ixekizumab exposure and the occurrence of SIs and IBD. The informativeness of comparative analyses depend on the number of patients available to analyse and the number of outcomes observed. Therefore, this phase of the study will depend on the results of Phase 1. If a sufficient number of exposures are identified, a formal comparative analysis will be conducted where we will calculate unadjusted and propensity score adjusted incidence rates (IR) and incidence rate ratios (IRR), with applicable 95% confidence intervals (CI) as appropriate for each individual outcome (Section 9.10).

9.4. Setting

The study population will include children (6 to less than 18 years of age) within a large, US administrative insurance claims database diagnosed with plaque psoriasis and exposed to ixekizumab or comparator medications: biologic medication (etanercept), non-biologic systemic medication (acitretin, cyclosporine, and methotrexate), and non-systemic topical treatment (corticosteroids, calcipotriene). If ixekizumab is approved for additional paediatric indications (e.g., psoriatic arthritis) during the study period, the study population will be expanded to include the new indications.

9.5. Inclusion and exclusion criteria

Inclusion Criteria

To be eligible for this study a patient must meet the following inclusion criteria:

- Age 6 to less than 18 years at the first dispensing of ixekizumab or comparator drug
- At least one diagnosis of plaque psoriasis before first dispensing of study medication

- At least one claim for ixekizumab or a comparator medication
- At least six months of continuous health plan eligibility before first dispensing of the study medication (first users of each medication).

Exclusion Criteria

Children will be excluded if they meet any of the following criteria:

- Children diagnosed during the baseline period with a disease listed below for which one or more of the drugs in this study is indicated:
  - Polyarticular juvenile idiopathic arthritis
  - Psoriatic arthritis
  - Ankylosing spondylitis
  - Ichthyoses
- Children who have history of an organ transplant.

9.6. Variables

9.6.1. Exposures

Defining exposure episodes for the primary and sensitivity analyses will depend on use of these medications in routine clinical practice. Therefore, preliminary work evaluating drug utilisation will be conducted before finalising exposure episodes. Exposure to ixekizumab or comparator medications will be identified from outpatient pharmacy claims using National Drug Codes (NDC), Generic Product Identifier (GPI), or drug administration procedure codes (e.g., Healthcare Common Procedure Coding System [HCPCS]), as applicable. Detailed information on ixekizumab and other medications used during the study period will be obtained, including dates of prescription/administration, dose, and duration of treatment.

Treatment episodes will be initiated by the first dispensing or administration of the study drug or comparator plus the number of days of supply/dosing interval and continue through five half-lives after the last dispensing or administration of the drug. If there is a gap between administrations/days' supply of the drug that is greater than five half-lives, that time will not be included in the exposed time period. However, the final definition of the treatment episode for the primary analysis will depend on use of these medications in routine clinical practice. Therefore, preliminary work evaluating drug utilisation will be done prior to finalising exposure episode. Additional detail regarding the definition of treatment episodes and management of treatment switching during the study period will be provided in the statistical analysis plan (SAP).

Drug of interest

- Ixekizumab

Comparator drugs

- Biologic
  - Etanercept

Like ixekizumab, etanercept is a biologic medication which was first approved in the US in 1998 and the EU in 2000, with approvals for paediatric psoriasis in the US in 2016 and in the EU in

2009. Etanercept is commonly used among children >6 years old with moderate-to-severe plaque psoriasis. Although ustekinumab and adalimumab are also approved to treat children with psoriasis in the US and EU, they are also indicated to treat IBD and therefore are not considered as comparators for this study. Recently, secukinumab has been indicated for moderate-to-severe paediatric plaque psoriasis in Europe but has not been approved by the Food and Drug Administration (FDA) and thus will not be included in our study.

Non-Biologic Systemics

- Acitretin
- Cyclosporine
- Methotrexate

Non-Systemic Topicals

- Corticosteroids
- Calcipotriene

Non-biologic drugs are commonly used for children with paediatric plaque psoriasis. These include acitretin, a non-immunosuppressing retinoid, and the immunosuppressants methotrexate and cyclosporine. None of these are FDA approved for psoriasis in children because of the lack of randomised controlled trials in this age category. Therefore, data on the risks and benefits of these non-biologic therapies come from long-term use in paediatric patients for conditions such as ichthyoses (acitretin), juvenile rheumatoid arthritis (methotrexate) and organ transplantation (cyclosporine) [10, 12]. A retrospective study using data from 2000 to 2014 found that among children with moderate-to-severe psoriasis, acitretin was the most frequently used therapy [13]. Non-systemic topicals are widely prescribed for mild cases of paediatric plaque psoriasis.

9.6.2. Outcomes

The study outcomes are serious infection and inflammatory bowel disease. In Phase 1, administrative claims data will be used to identify potential outcomes based on International Classification of Diseases, Tenth Revision (ICD-10) diagnosis and procedure, Common Procedural Terminology, and HCPCS codes. The codes and algorithms that will be used to identify the outcomes will be detailed in a separate SAP. Outcomes will be validated for the interim and final reports.

- Serious infection will be classified as follows:
  - Affected body system (e.g., respiratory tract, gastrointestinal tract, urinary tract, etc.)
  - Infections related to an injury or burn will not be included; the algorithm required to differentiate these injuries will be highlighted in the SAP.
- Inflammatory bowel disease will be identified from diagnoses of ulcerative colitis (UC) or Crohn's disease (CD) in a clinic, office, or hospital setting.

IBD is an episodic condition, thus we will categorise a diagnosis as 'new onset' if the child did not have any claims for IBD during the baseline period. If the child had a claim for IBD during the baseline period and another after a dispensation of a study treatment, this second diagnosis would be characterised as an 'exacerbation' of IBD. However, it is possible that a child could

have been diagnosed with IBD before entering our database and thus, it is possible that we may misclassify an exacerbation of IBD as a new case.

9.6.3. Covariates

Demographic and clinical information for patients including medical history, comorbidities, pre-existing medical conditions potentially related to increased risk of SI/IBD, and prior and concomitant medications will be examined. Plaque psoriasis and other relevant medical conditions are captured using the ICD-10 coding system as obtained from inpatient and outpatient medical claims. The use of medications before ixekizumab dispensing which may be markers for the presence or the severity of comorbid illness will be assessed. Prior use of medications for chronic medical conditions will be examined. Information on use of medications prescribed for the treatment of plaque psoriasis, and other chronic medical conditions will be extracted.

Baseline characteristics and demographic information will include:

- Demographic characteristics
  - Age (years)
  - US region of residence
  - Duration of health plan eligibility prior to dispensing
  - Calendar year of entry into the study

- Clinical characteristics
  - Autoimmune and inflammatory immune conditions
    - Plaque psoriasis
    - Lupus
    - Multiple sclerosis
    - Alopecia areata
    - Inflammatory bowel disease
  - Diabetes
  - Obesity
  - Hypertension
  - Depression
  - 10 most frequently occurring diagnoses recorded (for descriptive analyses)
- Medication use
  - Other medication used to treat plaque psoriasis, excluding those mentioned in Section 9.6.1 (e.g., phototherapy, biologic, and non-biologic therapies)
  - Immunosuppressants
  - 10 most frequently occurring medications recorded (for descriptive analyses)
- Healthcare utilisation (separately within the 6 months prior to the study)
  - Count of any office visits, emergency department visits, visits to a gastroenterologist, and hospitalisations
- Ixekizumab and comparator drug treatment characterisation (during the study period)
  - Duration of exposure
  - Treatment lines (i.e., observed treatment sequences in claims)

- Distribution of prior plaque psoriasis treatments.

9.7. Data Sources

This study will be conducted by HealthCore using the HIRD, a large administrative healthcare database maintained by HealthCore for use in health outcomes and pharmacoepidemiologic research. The HIRD is a longitudinal medical and pharmacy claims database from health plan members across the US. Member enrolment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory tests, and healthcare utilisation may be tracked for health plan members in the database dating back to January 2006, and with diagnoses recorded in ICD-10 since October 2015. Medical records will be obtained to validate outcomes as described in Section 9.10.3.

If uptake monitoring suggests that the number of ixekizumab-exposed children identified in the HIRD is below expected numbers outlined in Section 9.8, additional data sources will be incorporated. Exploration of other potential data sources will begin after protocol approval. If this approach is ultimately required, the protocol will be amended.

9.8. Study Size

The available number of exposed children will depend on the uptake of ixekizumab in the US among children between the ages of 6-<18 years. Preliminary feasibility counts from the HIRD indicate that biologic medications (etanercept and ustekinumab) are not widely used in paediatric psoriasis populations. Over a four-year period (2015-2019), there were approximately 580 paediatric psoriasis patients treated with a biologic, which, if divided equally among two available medications with steady accrual over 4 years would correspond to ~70 ((580/4 years)/2 medications) patients per medication, per year. No requirements for continuous health plan eligibility or other inclusion criteria were made in obtaining these preliminary counts. Although there remains a significant unmet medical need in this population, the uptake of a single medication such as ixekizumab is expected to occur more slowly than previously available biologic treatments and be impacted by the introduction of new medications to the marketplace. Available sample size will also be reduced by the requirement for continuous health plan eligibility, which is needed to assess baseline patient characteristics. Additionally, preliminary feasibility counts from the HIRD (2015-2019) indicate that non-biologic (N=2,551) and non-systemic medications (N>4,000) are more commonly prescribed in the paediatric population, allowing us to increase the ratio of comparator to ixekizumab for those two analyses. No requirements for continuous health plan eligibility or other inclusion criteria were made in obtaining these preliminary counts.

Assuming approximately 70 ixekizumab-exposed patients per year, this study will identify approximately 392 ixekizumab-exposed children from the time of the FDA paediatric indication approval (March 30, 2020) through the end of data collection (October 30, 2025). The lowest detectable relative risks with 80% power given a 1:1 etanercept:ixekizumab ratio for the study outcomes to be analyzed are described in Table 1. Table 1 also displays the lowest detectable relative risk with 80% power for estimated sample sizes given a 6:1 non-biologic comparator: ixekizumab and 9:1 non-systemic comparator: ixekizumab ratio for each of the study outcomes. All calculations assume a two-sided Type I error rate of 0.05 and baseline rates of serious infection and IBD in a paediatric population from the published literature [14, 15].

Table 1. Lowest Detectable Ixekizumab Relative Risk for Serious Infection and Inflammatory Bowel Disease

Comparator	Comparator to Ixekizumab Ratio	Lowest Detectable Relative Risk with 80% Power [c]	
		Serious Infection [a]	IBD [b]
Etanercept N=392	1:1	3.94	16.8
Non-Biologic N=2,352	6:1	2.9	8.9
Non-systemic N=3,528	9:1	2.82	8.5

Abbreviations: IBD = inflammatory bowel disease; N = number.

[a] Estimated background incidence 1% (over a 5-year period) [14]

[b] Estimated background incidence 0.1% (over a 5-year period) [15]

[c] These values were calculated using EpiSheet [16]

An interim report will be produced for delivery to the EMA by October 30, 2023. That report will contain uptake monitoring information for all study drugs, validated outcomes, and demographic information for all children who have been accrued into the study. In the case that the desired sample sizes are not reached in the HIRD by the second quarter of 2023, we will evaluate the feasibility of expanding the study population using additional data sources. Available data on uptake of the study drug and counts of outcomes will be summarised and reported in the interim and final reports.

9.9. Data Management

Datasets and analytic programs will be kept on a secure server and archived, per HealthCore record retention procedures. Full details concerning data security and quality assurance procedures will be captured in the SAP. Procedures for acquisition and abstraction of medical record data will be described in a medical record plan (MRP).

9.10. Data Analysis

9.10.1. Primary Analysis

In Phase 1, the number of children with exposure to ixekizumab, comparator drugs, and incidence of SI and IBD will be calculated. All cases of SI and IBD will be submitted for medical adjudication by clinical specialists and results of the validation will be presented in the interim and final reports. In order to achieve our target size by October 2025, we will assess uptake of the ixekizumab and comparator drugs at the end of second quarter of 2023 and determine if additional data sources need to be incorporated into the study or if the timeline for uptake monitoring needs to be extended. No additional analysis is planned for Phase 1.

In Phase 2, we will describe the number and percentage of children in each cohort for all of the demographic, clinical, treatment, and utilisation characteristics described in Section 9.6.3. Applicable baseline characteristics will then be used to calculate an exposure propensity score (PS) by modelling the probability of ixekizumab exposure versus the etanercept, non-biologic drugs, and non-systemic drugs (separately) as a function of the covariates [17]. Propensity score

matching will be used to balance risk factors for SI or IBD among ixekizumab-treated patients and each of the comparison groups. We will create separate propensity scores for SI and IBD as the risk factors for these outcomes are different. Propensity score matching uses variables identified as potential risk factors in the baseline period before the first dispensing of the drug of interest (e.g., age, geographic region, current comorbidities, and calendar time) as predictors of the choice of therapy. Propensity score matching produces groups that have similar distributions of variables included in the PS as well as any variables strongly associated with these covariates.

For each outcome (Section 9.6.2), we will describe the IR (calculated as the number of events divided by the person-time at risk). Incidence rate ratios (IRR) and corresponding 95% CIs will be calculated comparing children exposed to ixekizumab to children exposed to etanercept, children treated with non-biologic prescription medications, and children treated with topicals.

9.10.2. Exploratory Analysis

Exploratory analyses will be performed in which exposure ascertainment or outcome identification will vary from that in the primary analyses. Additional details will be provided in the SAP and MRP. Planned exploratory analyses include:

(1) Among children diagnosed with IBD, rates will be stratified by UC and CD.
(2) Among children diagnosed with SI, rates will be stratified by site impacted by infection.
(3) Among children prescribed non-biologic and non-systemic treatments, rates will be stratified by individual drug.
(4) In order to account for the impact of various treatment paradigms, we will conduct an intent to treat analysis where the first prescribed drug would be used as the exposure for the sensitivity analysis. Further details will be provided in the SAP.
(5) Beginning in March of 2020, the COVID-19 pandemic is expected to have an impact on how often patients have access to healthcare settings. To mitigate a potential threat to the validity of the study, we will conduct analyses stratified by before COVID, during COVID, and after COVID to understand the impact of the pandemic.

9.10.3. Validation

We will use medical records to validate claims diagnoses of the safety outcomes of interest. Medical records for children with IBD or SI diagnoses will be requested from providers and submitted to clinical experts for adjudication (blinded as to protected health information (PHI) and exposure status). We propose using two specialists to adjudicate each of the safety outcomes of interest. In the event of a disagreement among reviewers, we will review the basis for the disagreement jointly with the reviewers and determine a final classification. This evaluation will assess the positive predictive value (PPV) of the SI and IBD algorithm in claims data. Records will be sought for all patients who have experienced SI and IBD based on the case definition. The average retrieval rate for medical records is about 65-70%. We will use estimates of PPV and plausible values of sensitivity by treatment group to inform a quantitative bias analysis. Details of the medical adjudication and quantitative bias analysis will be provided in a separate MRP and SAP.

9.11. Quality Control

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits of the data, accuracy and consistency of collected data, validation of coding, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. Written programming will be reviewed independently. The secure storage of data, study programs, log files, output files, and back-up will be ensured as required by regulatory guidelines. All key study documents will undergo quality control and review.

The study will be executed in line with all applicable regulations and guidelines, such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology, as well as the data vendor's quality management system.

9.12. Limitations of the Research Methods

The 2019–20 coronavirus pandemic is currently influencing all areas of clinical care, including changes to health clinic operations and changing patients' perceptions of the risks and benefits involved in seeking care. Though the complete impact of medical record retrieval is unknown, we hypothesise that patients may delay or cancel important screening procedures or fail to seek care for acute conditions out of fear of catching the virus by leaving their home. These circumstances may impact the uptake of ixekizumab among patients in the HIRD. This may require additional time or partnering with other data sources in order to achieve the required sample size. HealthCore is prepared to serve as the data coordinating centre in a multi-database study should this be required in order to achieve the desired sample size.

This study integrates a large claims database with medical record review to conduct safety analyses of ixekizumab. To control for confounding by indication, we selected children being treated with medications approved for the same diagnosis as ixekizumab as comparators (etanercept and non-biologics). Doing so enhances comparability on diagnosis, and on unmeasured factors related to diagnosis that may also be related to outcomes. In addition, medical history and utilisation recorded in the claims data will be used to compute propensity scores to further enhance comparability. Despite these efforts, there is potential for residual confounding by covariates not captured or captured inaccurately in automated claims. Additionally, because this study has composite endpoints, the association between ixekizumab and a composite endpoint may be different than the association for a more specific condition included in the composite endpoint. In other words, if there is an effect of ixekizumab that is not uniform across all endpoints included in the composite, the effect of the outcome that is associated with ixekizumab may be partially masked by other conditions that are included in the outcome definition but not associated with ixekizumab use. If a component endpoint is elevated, however, the composite endpoint also will be elevated although to a lesser degree, due to this misclassification. Therefore, we will conduct a series of sensitivity analyses (Section 9.10.1) in order to better elucidate the impact of some of these potential sources of confounding on our main analysis.

Another limitation of this study is the use of non-systemic topical treatments as a comparator group for a biologic medication indicated for children with moderate-to-severe paediatric plaque psoriasis. Patients prescribed non-systemic topical medication might be expected to have a milder form of the disease or not be appropriate candidates for biologic medications due to other comorbidities. Thus, we expect reduced comparability between the children in the ixekizumab and non-systemic topicals groups. Any differences in disease severity and indications for the non-systemic topicals between treatment groups introduces potential confounding bias that must be considered when interpreting the results of this study.

The main limitations relate to uncertainties regarding the numbers of subjects available to study for a new medication, and limitations inherent in database studies, including accuracy of codes used to identify outcomes. Also, uptake of a new product (plus the follow-up time necessary to observe events) will determine the time at which a sufficient study size for analysis will be accrued in the database, as discussed in Section 9.8. Additionally, the sample size for this study was calculated based on the number of children in the HIRD (between 2015-2019) with moderate-to-severe plaque psoriasis who were prescribed biologic medications. Given the rare occurrence of moderate-to-severe paediatric plaque psoriasis requiring biologic medications, this study is planned for a sample size to detect a 16.8-fold difference in risk of IBD among children

prescribed ixekizumab versus etanercept. However, among children who were prescribed non-biologics as compared to those prescribed ixekizumab, the study will have the sample size to detect ≥8.9-fold increase in risk for IBD. Furthermore, because SI is more prevalent than IBD, the planned sample size will allow us to detect a ≥3.9-fold difference in risk for SI among children who were prescribed ixekizumab, compared to those who were prescribed etanercept.

Although outcomes will be verified by medical record review, exposure, outcome, or covariate misclassification may present issues in the Phase 2 cohort surveillance study. For example, we will rely on pharmacy dispensing data to determine whether patients used medications, however it is possible that a medication was purchased but not used, which can lead to exposure misclassification. Likewise, verification of outcomes in the administrative claims will be limited to those outcomes that can be identified in the medical record. For example, a mild case of IBD may never come to medical attention, and therefore our outcome is limited to those situations where the patient seeks medical care. Finally, information on certain potential confounding variables of interest is not available or poorly documented in administrative claims data, potentially resulting in covariate misclassification. Not all the outcomes of interest have been validated in administrative claims data, and the performance of ICD-10 codes, which have been used only since October 2015 in the US, has not been well characterised in this setting. As such, we expect that the number of outcomes identified via administrative claims in Phase 1 uptake monitoring will differ from the number of outcomes verified by medical record review. Although PPV and sensitivity of algorithms based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes have been studied for some outcomes, their performance must be further evaluated and updated for ICD-10 codes [18].

Although use of medical record verification of IBD and SI present important strengths of the study, it should be recognised that it will not be possible to obtain medical records for all children, for example, in cases where a facility may not honour the Ethical Review Board waiver of Health Insurance Portability and Accountability Act authorisation due to institutional policies and refuse to provide the requested medical record. There may also be cases where a medical record is provided that does not capture the requested history. In other cases, a patient may seek care from an out of network provider, for example, the provider is not identifiable in the administrative claims data. Although every attempt will be made to obtain complete records for children, as will be detailed in the SAP, incomplete capture of the cohort may affect validation if those for whom medical record data are unavailable or incomplete differ in important ways from those who can be included.

9.13. Other Aspects

Not applicable.

10. Protection of Human Subjects

Observational studies will be submitted to ethical review boards (ERBs) for approval whenever required by local law. In addition, regardless of local law, all primary data collection observational studies will be submitted to at least 1 independent body (for example, ERB) per country for review and to confirm that the study is considered non-interventional in that country. Regulatory authorities will be notified, and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

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

11. Management and Reporting of Adverse Events/Adverse Reactions

This is a non-interventional study based on secondary data use, and therefore no individual case safety report reporting is required. The study protocol-defined adverse events (AEs) are described in Section 9.6.2. All protocol-defined AEs collected will be summarised in the interim and final study reports. No other AEs will be collected.

12. Plans for Disseminating and Communicating Study Results

Final reports will be submitted to regulatory agencies. The study, including the final report, will also be registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Registry. Results from Phase 2 may be disseminated via presentation at scientific conferences and/or publication in peer-reviewed journals.

13. References

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4. Tollefson, M.M., et al., *Incidence of psoriasis in children: a population-based study.* J Am Acad Dermatol, 2010. **62**(6): p. 979-87.
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Annex 1. List of Standalone Documents

None.

Annex 2. ENCePP Checklist for Study Protocols

Study title:

Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Paediatric Psoriasis

EU PAS Register® number: EUPAS36306

Study reference number (if applicable): I1F-MC-B015

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

[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.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				Section 8
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)	☒	☐	☐	Section 8
2.1.2 The objective(s) of the study?	☒	☐	☐	Section 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Section 8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	Section 8

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, other design)	☒	☐	☐	Section 9
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	Section 9
3.3 Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒	☐	☐	Section 9
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	Section 9
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)	☒	☐	☐	Section 11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	Section 9.4
4.2 Is the planned study population defined in terms of:				Section 9
4.2.1 Study time period	☒	☐	☐	
4.2.2 Age and sex	☒	☐	☐	
4.2.3 Country of origin	☒	☐	☐	
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Section 9

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)	☒	☐	☐	Section 9
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	Section 9
5.3 Is exposure categorised according to time windows?	☒	☐	☐	Section 9
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	Section 9
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	Section 9
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	Section 9

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?	☒	☐	☐	Section 9
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Section 9
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	Section 9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	Section 9.12
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	Section 9.12
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	Section 9.12

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	Section 9

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)	☒	☐	☐	Section 9
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Section 9
9.1.3 Covariates and other characteristics?	☒	☐	☐	Section 9
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)	☒	☐	☐	Section 9
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 9

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	Section 9
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Section 9
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Section 9
9.3.3 Covariates and other characteristics?	☒	☐	☐	Section 9
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	Section 9

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	Section 9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	Section 9
10.3 Are descriptive analyses included?	☒	☐	☐	Section 9
10.4 Are stratified analyses included?	☒	☐	☐	Section 9
10.5 Does the plan describe methods for analytical control of confounding?	☒	☐	☐	Section 9.12
10.6 Does the plan describe methods for analytical control of outcome misclassification?	☒	☐	☐	Section 9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	Section 9
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	Section 9

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)	☒	☐	☐	Section 9.11
11.2	Are methods of quality assurance described?	☒	☐	☐	Section 9.11
11.3	Is there a system in place for independent review of study results?	☒	☐	☐	Section 9.11

Comments:

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?	☒	☐	☐	Section 9.12
	12.1.2 Information bias?	☒	☐	☐	Section 9.12
	12.1.3 Residual/unmeasured confounding?	☒	☐	☐	Section 9.12
	(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2	Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	Section 9

Comments:

Section 13: Ethical/data protection issues		**Yes**	**No**	**N/A**	**Section Number**
13.1	Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	Section 10
13.2	Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	Section 10
13.3	Have data protection requirements been described?	☒	☐	☐	Section 9.11

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Section 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)?	☒	☐	☐	Section 12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Section 12

Comments:

Name of the main author of the protocol: _PPD

Date: 10/12/2020

Signature: ___ PPD

Annex 3. Additional Information

None.