PASS Information

Title	I1F-EW-B008: Assessing the Safety of Ixekizumab in European Psoriasis Registries
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Date of last version	Not applicable
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Product reference	EMEA/H/C/003943
Procedure number	Not applicable
Marketing Authorization Holder(s)	Eli Lilly Nederland B.V.
Joint PASS	No
Research question and objectives	The objective of this study is to perform safety surveillance by monitoring the incidence of adverse events occurring in temporal association with ixekizumab among patients with psoriasis enrolled in 2 European biologic registries.
Country(-ies) of study	United Kingdom, Germany
Author	PPD Eli Lilly and Company Lilly Corporate Center, Indianapolis, IN 46285, United States PPD

Marketing Authorization Holder

Marketing Authorization Holder (MAH)	Eli Lilly Nederland B.V.
MAH contact person	PPD ; Eli Lilly and Company Lilly Corporate Center, Indianapolis, IN 46285, United States PPD

1. Table of Contents

Section **Page**

List of Tables

List of Annexes

2. List of Abbreviations

Term	Definition
AE	adverse event
BADBIR	British Association of Dermatology Biologics Intervention Register
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
IL	interleukin
Lilly	Eli Lilly and Company
MAH	Marketing Authorization Holder
SAE	serious adverse event

3. Responsible Parties

Registry operations for the British Association of Dermatology Biologics Intervention Register (BADBIR) are carried out by the University of Manchester, while the British Association of Dermatologists provides independent review and oversite. Registry operations for PsoBest, the German psoriasis registry, are carried out by Universitätsklinikum Hamburg-Eppendorf.

4. Abstract

Title

I1F-EW-B008: Assessing the Safety of Ixekizumab in European Psoriasis Registries

Version: 0.1

Main author: PPD Eli Lilly and Company

Rationale and Background

Ixekizumab is a selective interleukin (IL)-17A receptor inhibitor recently approved in Europe and other countries for the treatment of moderate to severe psoriasis. Data from clinical studies in patients with psoriasis demonstrate that ixekizumab is effective and generally well tolerated; however, the pattern of use and effectiveness in routine clinical practice has not been characterized. Prospective disease state registries provide an opportunity to study new medications in real-world populations. Eli Lilly and Company (Lilly) is sponsoring the enrollment of ixekizumab patients into two European psoriasis registries (BADBIR and PsoBest) to obtain data, including treatment patterns and effectiveness of ixekizumab, in the real world. The registries will also provide safety information. Although the safety data will be limited, it will be reviewed within the context of ixekizumab's global safety data and used to perform safety surveillance. This protocol focuses on the safety information, outlining the data that will be received from the registries and how it will be interpreted. The protocol may be amended in the future to accommodate additional registries.

Research Questions and Objectives

The objective of this study is to perform safety surveillance by monitoring the incidence of adverse events (AEs) occurring in temporal association with ixekizumab among patients with psoriasis enrolled in two European biologic registries.

Study Design

Data from two independent European registries will be reviewed to provide information about the safety of ixekizumab. The registries included in this study are BADBIR and the German psoriasis registry PsoBest. BADBIR and PsoBest are prospective cohorts, collecting data on enrolled patients at regular intervals. Registry protocols and operations are independent of Lilly and are not typically tailored to individual molecules.

Population

This study includes patients with psoriasis from the BADBIR and PsoBest registries.

Variables

Exposure: Each registry assigns exposure time to a cohort based on the medication classification as presented in Table 2. Cohort definitions vary across the registries. For both registries, exposure is reported by the physician at baseline and at subsequent follow-up visits. The cohorts

described below represent groups that will be captured in standard reports to Lilly, but do not necessarily represent all cohorts available in the registry.

BADBIR Cohorts:

Ixekizumab Cohort: Patients with moderate to severe psoriasis starting on or switching to therapy with ixekizumab

Control Cohort: Biologic-naïve patients with moderate to severe psoriasis starting on or switching to a conventional systemic medication

PsoBest Cohorts:

Ixekizumab Cohort: Patients with moderate to severe psoriasis, with or without arthritis, initiating treatment with ixekizumab

Biologic Cohort: Patients with moderate to severe psoriasis, with or without arthritis, newly initiating a biologic medication (excluding ixekizumab)

Systemic Cohort: Patients with moderate to severe psoriasis, with or without arthritis, newly initiating a traditional systemic medication

Outcomes: BADBIR and PsoBest provide standard reports containing safety outcomes. The BADBIR report will provide data on pre-specified outcomes including serious infections, cardiac disorders, central nervous system disorders, hematologic events, malignancy, pregnancy, and death. Cancer and malignancy outcomes are confirmed via linkage with national registries. The PsoBest report will contain a listing of all AEs reported, aggregated by cohort and organized by the Medical Dictionary for Regulatory Activities System Organ Class.

Covariates: Each registry collects information on psoriasis disease severity, concomitant medication use, and comorbidities; however, much of this information is omitted from the standard reports and is reserved for use by the registries.

Data Sources

All data for this study will be obtained from standard reports provided by the BADBIR and PsoBest registries.

Ixekizumab Sample Size

The enrollment of ixekizumab-exposed patients into BADBIR and PsoBest will depend on multiple factors including:

- The registry's recruitment procedures and activities
- Recommendation of local government agencies or scientific groups that ixekizumab should be registered
- The uptake of ixekizumab in each country.

The number of ixekizumab and comparator patients will vary between registries, as will the duration of follow-up. Consequently, the power to detect differences in risk between cohorts will also vary.

The standard BADBIR agreement is a 5-year recruitment period, followed by 4 years of follow-up, resulting in a maximum follow-up of 9 years for individuals enrolled in the first year. The registry anticipates monitoring approximately 2000 ixekizumab patients during the 5-year enrollment period. The PsoBest standard agreement is to enroll a maximum of 500 patients per year for a total of 5 years. No registry reports will provided to Lilly after the 5-year contract.

Data Analysis

Analysis of BADBIR and PsoBest data is under the control of each individual registry and will not include input from Lilly. The results of data collection and analyses will be delivered to Lilly as a standard report.

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned date
Start of Data Collection	BADBIR: Q2 2017 PsoBest: Q1 2017
End of Data Collection	BADBIR: Q4 2025 PsoBest: Q1 2022
Final report of study results	Q4 2027

7. Rationale and Background

Psoriasis is a common chronic, immune-mediated inflammatory skin disorder that requires long-term treatment. In Western countries, psoriasis is estimated to affect 2% to 4% of the population (Parisi et al. 2013). Plaque psoriasis (hereafter psoriasis) is the most common form of psoriasis and was shown to have a significant impact on the overall health of patients (Feldman et al. 2016). Approximately 20% to 33% of patients with psoriasis suffer from moderate to severe disease (Menter et al, 2008). European treatment recommendations for moderate to severe disease are phototherapy and systemic therapies, including biologics, alone or in combination (Mrowietz et al. 2011).

In recent years, a number of new biologics have been approved for the treatment of moderate to severe psoriasis, including ixekizumab, a selective IL-17A inhibitor. Although clinical trials provide valuable information on the safety and efficacy of ixekizumab, the need to understand the use among patients in routine clinical practice, particularly in Europe, remains. Prospective disease state registries provide an opportunity to study new medications outside of the clinical trial setting. Lilly is subscribing to two European Psoriasis registries (BADBIR and PsoBest) to obtain real-world data including treatment patterns and effectiveness of ixekizumab in the real world. The registries will also provide safety information. Although the safety data will be limited, it will be reviewed within the context of global safety data and used to perform safety surveillance. This protocol focuses on the safety information, outlining the data that will be received from the registries and how it will be interpreted.

8. Research Questions and Objectives

The objective of this study is to perform safety surveillance by monitoring the incidence of AEs occurring in temporal association with ixekizumab among patients with psoriasis enrolled in two European biologic registries. This document will be amended as additional registries are joined.

9. Research Methods

9.1. Study Design

Data from two independent European registries will be reviewed to provide information about the safety of ixekizumab. The registries included in this study are BADBIR and the German psoriasis registry PsoBest. BADBIR and PsoBest are cohorts that perform prospective primary data collection on enrolled patients. The target populations are patients with psoriasis in the respective countries. Registry protocols and operations are independent of Lilly and are not typically tailored to individual molecules.

9.2. Setting

9.2.1. BADBIR

BADBIR is a national registry of patients with psoriasis treated with conventional systemic therapy (Comparator cohort) or biologic agents. The primary purpose of the registry is to evaluate the long-term safety of biologics in the treatment of psoriasis. Secondary aims of BADBIR include collecting information about the long-term effectiveness of these therapies, the effects of conventional and biologic treatment sequence, and the outcomes of pregnancies occurring during treatment. Enrollment of patients with psoriasis receiving biologics into BADBIR is recommended by the UK guidelines and the National Institute for Health and Clinical Excellence (Burden et al. 2012). As a result, the registry is highly representative of patients with psoriasis treated with biologic agents. The first ixekizumab-exposed patient entered the registry in May 2017.

Eligibility for the registry includes individuals older than 16 years receiving a diagnosis of psoriasis from a dermatologist. For patients in the Biologic or Ixekizumab cohort, individuals must have started on or switched to the biologic within the previous 6 months. Patients in the systemic therapy comparator cohort must be biologic naïve, started on or switched to a conventional systemic medication within the previous 6 months, and must have a Psoriasis Area and Severity Index and Dermatology Life Quality Index ≥10. All registry patients must provide informed consent. Patients are then followed up to 5 years, regardless of medication switches or terminations. Clinical information is collected by the treating physician every 6 months for the first 3 years and then annually until the end of Year 5. Patients are also provided with a diary for use between visits to record details of changes in drug therapy, hospital consultant referrals, and hospital admissions (Burden et al. 2012).

Several pharmaceutical companies sponsor the BADBIR registry. The BADBIR Research Governance: Stakeholder Accountabilities and Responsibilities fully outlines the responsibilities of the pharmaceutical sponsors (BADBIR Registry [WWW]). A list of all pharmaceutical sponsors can be obtained from the registry directly.

9.2.2. PsoBest

Similar to BADBIR, PsoBest is also a national registry with the purpose of investigating the long-term safety and effectiveness of medications used in the treatment of psoriasis. In Germany, there are no regulations for prescribing biologic medications; however, European guidelines on the systemic treatment of psoriasis suggest that these medications be used in patients with moderate to severe disease who experienced an inadequate response to traditional systemic treatment, or if traditional systemic treatment is contraindicated or not tolerated (Pathirana et al. 2009). These recommendations are reflected in the registry eligibility criteria, which include adult patients with moderate to severe psoriasis with and without arthritis initiating a conventional systemic therapy or a biologic agent (Augustin et al. 2014). All registry patients must provide informed consent. Patients are then followed for 10 years regardless of medication switches or terminations; however, follow-up information is only shared with pharmaceutical companies for the duration of the contract. Follow-up visits in the dermatology office are conducted every 3 months in the first half-year and every 6 months thereafter. In addition, 3 months after the physician visits, patients are contacted by mail for further information on treatment status and patient-reported outcomes (Reich et al. 2015).

Several pharmaceutical companies sponsor the PsoBest registry. A current list of pharmaceutical sponsors can be found at the clinicaltrials.gov website. (Psobest Registry, 2017).

9.3. Variables

9.3.1. Drug Exposure

Each registry assigns exposure time to a cohort (Table 1) based on the medication classification presented in (Table 2). Cohort definitions vary across the registries. For both registries, exposure is reported by the physician at baseline and at subsequent follow-up visits. The cohorts described below represent groups that will be captured in standard reports to Lilly, but do not necessarily represent all cohorts available in the registry.

Table 1. Drug Exposure Cohort Definitions for BADBIR and PsoBest

Registry	Cohort	Cohort Definition
BADBIR	Ixekizumab Cohort	Patients with moderate to severe psoriasis starting on or switching to therapy with ixekizumab
	Control Cohort	Biologic-naïve patients with moderate to severe psoriasis starting on or switching to a conventional systemic medication
PsoBest	Ixekizumab Cohort	Patients with moderate to severe psoriasis, with or without psoriasis, newly initiating ixekizumab
	Biologic Cohort	Patients with moderate to severe psoriasis, with or without arthritis, newly initiating a biologic medication (excluding ixekizumab)
	Systemic Cohort	Patients with moderate to severe psoriasis, with or without arthritis, newly initiating a traditional systemic medication

Abbreviation: BADBIR = British Association of Dermatology Biologics Intervention Register.

Table 2. Traditional Systemic and Biologic Medication

BADBIR Control Cohort	PsoBest Systemic Cohort	PsoBest Biologic Cohort
Acitretin	Acitretin	Adalimumab
Ciclosporin	Ciclosporin	Etanercept
Fumaric acid esters	Fumaric acid esters	Infliximab
Hydroxycarbamide	Methotrexate	Secukinumab
Methotrexate	Apremilast	Ustekinumab
PUVA		

Abbreviation: BADBIR = British Association of Dermatology Biologics Intervention Register.

In the BADBIR and PsoBest registries, serious events are assigned to the drug (and reported to corresponding pharmaceutical company) that the patient is receiving at the time of the event. If an event occurs 90 days after the termination of a biologic drug, no event is reported. These additional days constitute a risk window in which patients can accrue additional time at risk after the termination of a medication. If an event occurs within the 90-day risk window, the event will be assigned to the terminated drug and reported to the corresponding company. In the instance that a patient switches medication within the risk window, the event will be reported to both companies. Exceptions to these reporting rules include cases of pregnancy, malignancy, and death. For each of these events, complete biologic history will be taken into account and the event will be reported, even if the 90-day risk window has passed. In the PsoBest registry, events occurring within a combined treatment are assigned to all treatments (Reich et al. 2015; BADBIR Pharmacovigilance SOP 2017).

9.3.2. Outcomes

BADBIR and PsoBest provide standard reports containing safety outcomes. The BADBIR report will follow the BADBIR Company Report Template (Annex 2) and will provide data on the pre-specified outcomes outlined in Table 3. Cancer and malignancy outcomes are confirmed via linkage with national registries to reduce information bias (Burden et al. 2012). The PsoBest report will contain a listing of all AEs reported, aggregated by cohort and organized by the Medical Dictionary for Regulatory Activities System Organ Class.

9.3.3. Covariates

Each registry collects information on psoriasis disease severity, concomitant medication use, and comorbidities; however, much of this information is omitted from the standard reports and is reserved for use by the registries.

Table 3. Safety Outcomes Provided in the Standard BADBIR Report (Manchester Template)

Serious Infections[a]	Cardiac Disorders	Central Nervous System Disorders	Hematologic Events	Malignancy	Other
Total serious infection	Total cardiac disorders	Total CNS disorders	Total hematologic events	Total malignancy events	Pregnancy
Pneumonia	Congestive heart failure (new or worsening)	Demyelination	Aplastic anemia	Lymphoproliferative	Death
Septicemia	Myocardial infarction	Peripheral neuropathy	Pancytopenia	Lymphoma (non-Hodgkin's, Hodgkin's)	
Septicemia (site-specific infection)	Other cardiac events	Other CNS disorders	Agranulocytosis	Myeloma	
Bone/joint infection			Other dyscrasia	Leukemia	
Opportunistic infection				Non-melanoma skin cancer	
Other serious infection				Other malignant solid tumors	
Tuberculosis					

Abbreviations: CNS = central nervous system; IV = intravenous.

[a] A serious adverse event or reaction is an untoward medical occurrence that is considered to represent a significant hazard to the patient. This definition is derived from regulatory authorities, including the European Medicines Agency and the US Food and Drug Administration, and includes the following events : death, immediately life-threatening, require overnight hospitalization (initial or prolonged), require IV antibiotics/IV anti-viral or IV anti-fungal medications, result in significant loss of function or disability or a congenital malformation/birth defect, or are considered medically important (malignancies and pregnancy).

9.4. Data Sources

All data for this study will be obtained from standard reports provided by the BADBIR and PsoBest registries. Standard reports are non-negotiable. A description of standard report content is provided in Section 9.7.

In addition to the standard report, BADBIR will also provide a dataset containing anonymized observations for patients in the Ixekizumab Cohort and Control Cohort. Safety observations are not included in this dataset. Protocols for use of this data will be developed separately.

9.5. Study Size

The inclusion of ixekizumab-exposed patients into BADBIR and PsoBest will depend on multiple factors including:

- The registry's inclusion procedures and activities
- Recommendation of local government agencies or scientific groups that ixekizumab should be registered
- The market uptake of ixekizumab in each country

The number of ixekizumab and comparator patients will vary between registries, as will the duration of follow-up. Consequently, the power to detect differences in risk between cohorts will also vary. The number of hypotheses that can be investigated will increase as the recruitment of ixekizumab increases. Table 4 summarizes the estimated number of ixekizumab patient-years needed to achieve 80% power (assuming 1:1 ratio of ixekizumab patients to comparator patients) to detect various magnitudes of risk among ixekizumab patients relative to comparator group for 2 outcomes investigated by both registries.

Table 4. Estimated Number of Ixekizumab-Exposed Patient-Years Needed to Achieve 80% Power to Detect Various Magnitudes of Risk among Ixekizumab-Exposed Patients Relative to a Comparator Group

		Relative Risk			
		1.5	2.0	2.5	3.0
Outcome	**Estimated Incidence (per 100 patient-years)**	**Number of Patient-Years of Ixekizumab Exposure Needed**			
Serious infection	1.4	4417	1325	687	442
Malignancy (excluding NMSC)	0.61	10,136	3041	1576	1014

The standard BADBIR agreement is a 5-year recruitment period, followed by 4 years of follow-up, resulting in a maximum follow-up of 9 years for individuals enrolled in the first year. The registry anticipates enrolling approximately 2000 patients during the 5-year enrollment period. The PsoBest standard agreement is to recruit a maximum of 500 patients per year for a total of 5 years. No registry reports will provided to Lilly after the 5-year contract.

9.6. Data Management

Data management procedures vary by registry and are available from the registries directly.

9.7. Data Analysis

Analysis of BADBIR and PsoBest data is under the control of each registry and will not include input from Lilly. The results of some analyses will be provided to Lilly as a standard report. Registries may also conduct analyses beyond the scope of the standard report. Results from these analyses may not be shared with Lilly. The following sections provide details about the reports that will be received.

9.7.1. BADBIR

As part of the standard agreement with BADBIR, Lilly will receive a 6-monthly report, an interim report, and a final report. The 6-monthly report will contain cumulative rates of safety outcomes (Table 3) for the Ixekizumab Cohort and Control Cohort, organized according to the BADBIR Template (Annex 2). Analysis for the interim report is expected to start when 5000 patient-years of exposure have accrued. The final report is expected 1 year after receipt of the last standard report. Both the interim and final reports will contain comparative analyses between Ixekizumab Cohort and the Control Cohort, adjusted for baseline and other differences. The BADBIR final report will contain formal hypothesis tests comparing ixekizumab-exposed patients and control patients with respect to the incidence of malignancy, serious infections, any serious adverse event (SAE) other than death, and death (primary outcomes). No additional information on the analyses is provided by BADBIR.

9.7.2. PsoBest

Similar to BADBIR, RABBIT also provides semiannual reports as part of the standard agreement. The report will contain a listing of all AEs reported, aggregated by cohort and organized by the Medical Dictionary for Regulatory Activities System Organ Class. PsoBest will also perform a retrospective analysis of clinical and epidemiological baseline data. No final report will be provided, per registry standard procedure. No additional information on the analyses is provided by BADBIR.

9.8. Quality Control

Quality control processes are registry dependent. Information on these processes can be obtained directly from the registries.

9.9. Limitations of Research Methods

9.9.1. Registry Size

BADBIR and PsoBest are large registries reporting on more than 8000 and 2500 patients with psoriasis, respectively (Eissing et al. 2016); however, the Ixekizumab Cohort in each individual registry is not expected to be large enough to evaluate rare, but important safety, outcomes of interest. A potential solution to examine rare outcomes is to evaluate data across registries, performing nested case-control studies and undertaking a meta-analysis of the results (Zink et al. 2009). For this approach to be successful, however, it is important to coordinate analyses of the individual registry data to ensure that results can be analyzed together. Currently, BADBIR and PsoBest will only provide reports outlined in Section 4, preventing a meta-analysis. The registries may capture a sufficient number of patients to detect moderate to large relative risks in common events. Therefore, the data received from the registries will be used for safety surveillance and will be evaluated within the context of ixekizumab global safety data.

9.9.2. Comparator Cohorts

Typically, patients with psoriasis treated with biologics have severe or long-standing disease. Disease severity is associated with greater comorbidity and risk for AEs, independent of treatment. Comparisons between the Ixekizumab Cohort and the Control Cohort in the BADBIR final report may be confounded by disease severity, even after adjustment for baseline differences if there is not sufficient overlap between the two populations. Residual confounding may also be present if there are imbalances in other risk factors that cannot be adequately addressed.

PsoBest will not provide a comparative report. Instead, a semiannual report comprising of crude cumulative incidence rates and 95% confidence intervals will be provided. These results should be interpreted with caution. The incidence rates presented in these reports reflect interim data from ongoing studies. At the time of reporting, not all AEs or person-time experience may have been completely captured. Also, because of the potential presence of channeling bias, any crude comparisons of incidence rates for the Ixekizumab Cohort and Comparator Cohort should be made with caution.

9.9.3. Inability to Modify Data Collection or Analyses

BADBIR and PsoBest are prospective registries that receive funding from pharmaceutical companies, but operate independently, restricting industry sponsors ability to modify data collection or analyses. Without the provision of a detailed statistical analysis plan, it is unclear if there will be missing confounders in the descriptive reports or final comparative analyses. A review of registry output will help us address this in the final study report. The lack of input into the registries also limits the utility of using registry data to address scientific questions or regulatory requests.

9.10. Other Aspects

None

10. Protection of Human Subjects

University of Manchester (BADBIR) and Universitätsklinikum Hamburg-Eppendorf (PsoBest) have received ethical approvals as required by applicable laws and regulations in the United Kingdom and Germany.

11. Management and Reporting of Adverse Events/Adverse Reactions

The BADBIR registry instructs investigators or study personnel to collect, per registry procedures, any registry protocol-defined AEs and AEs of special interest, including all associated fatal outcomes, occurring in temporal association with Lilly product(s). Pregnancy exposure does not meet the definition of an AE; however, it is collected per registry procedures. AEs other than the registry protocol-specified AEs and events of special interest will not be actively collected, as these are not part of the registry objectives. SAEs will be reported to Lilly, via an approved method, within 24 hours. Protocol-defined AEs will be forwarded to Lilly within 24 hours. Non-SAEs not specified in the protocol as well as product complaints will be reported in normal practice, as required by applicable laws and regulations.

The PsoBest registry collects information on all reported AEs and SAEs. Investigators are instructed, per the PsoBest registry protocol, to report all SAEs to the registry within 24 workday hours. Investigators must also forward reports to the competent authorities. The registry is then responsible for forwarding SAE reports to Lilly, within a timeframe of 24 workday hours after plausibility and minimum criteria have been positively checked. Events that may not be immediately life-threatening but may jeopardize the subject or may require intervention to prevent a serious outcome and pregnancies will be reported as a SAE. Product complaints will be reported in normal practice, as required by applicable laws and regulations.

12. Plans for Disseminating and Communicating Study Results

This study will be registered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) EU PAS (the European Union electronic Register of Post-Authorisation Studies) register. A completed ENCePP Checklist for study protocols is attached in Annex 2. Any substantial amendments to the study protocol or final study report will be entered in the register. Data from registry reports may be disseminated via presentation at scientific conferences and/or publication in a peer-reviewed journal.

13. References

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Annex 1. ENCePP Checklist for Study Protocols

Study title:

I1F-EW-B008: Assessing the Safety of Ixekizumab in European Psoriasis Registries

Study reference number:

EUPAS21980

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				6
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☒	☐	☐	
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:

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 (eg, to address an				

[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**
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 and 9.2
2.1.3 The target population (ie, population or subgroup to whom the study results are intended to be generalized)?	☒	☐	☐	9
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	9
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

This protocol describes the *a priori* registry hypotheses and the use of these reports to perform safety surveillance.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described (eg, 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?	☒	☐	☐	9.2
3.3 Does the protocol specify measures of occurrence (eg, incidence rate, absolute risk)?	☒	☐	☐	8
3.4 Does the protocol specify measure(s) of association (eg, relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm per year)?	☒	☐	☐	9.5
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions (eg, adverse events that will not be collected in	☒	☐	☐	11

Section 3: Study design	Yes	No	N/A	Section Number
case of primary data collection)?				

Comments:

This protocol describes study design as presented in the registry contracts and protocols.

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:	☒	☐	☐	6 and 9.2
4.2.1 Study time period?	☐	☐	☒	N/A
4.2.2 Age and sex?	☒	☐	☐	9.1 and 9.2
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	9.2
4.2.5 Duration of follow-up?				
4.3 Does the protocol define how the study population will be sampled from the source population (eg, event or inclusion/exclusion criteria)?	☒	☐	☐	9.2

Comments:

This protocol describes source and study populations as presented in the registry protocols and publications.

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 (eg, operational details for defining and categorizing exposure, measurement of dose, and	☒	☐	☐	9.3

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
duration of drug exposure)?				
5.2 Does the protocol address the validity of the exposure measurement (eg, precision, accuracy, use of validation sub-study)?	☒	☐	☐	9.3
5.3 Is exposure classified according to time windows (eg, current user, former user, non-use)?	☒	☐	☐	9.3
5.4 Is exposure classified based on biologic mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3

Comments:

This protocol describes exposure definition and measurements as presented in the registry protocols and publications.

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 and 9.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement (eg, precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)?	☒	☐	☐	9.3
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment (eg, HRQoL, QALYs, DALYS, health care services utilization, burden of disease, disease management)?	☐	☐	☒	NA

Comments:

This protocol describes outcome definition and measurements as presented in the registry contracts and protocols.

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
7.1.1 Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7
7.2 Does the protocol address:				
7.2.1 Selection biases (eg, healthy user bias)?	☐	☐	☒	N/A
7.2.2 Information biases (eg, misclassification of exposure and endpoints, time-related bias)?	☒	☐	☐	9.3
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	N/A

Comments:

This protocol describes how confounding will be addressed as presented in the registry protocols and publications. Selection bias is not anticipated due to the population-based nature of these registries. Validity of study covariates is not addressed in the registry protocols.

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

Comments:

The registry protocols do not address effect modification.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**

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 (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)?	☒	☐	☐	9.3
9.1.2 Outcomes (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)?	☒	☐	☐	9.3
9.1.3 Covariates?	☒	☐	☐	9.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)?	☒	☐	☐	9.3
9.2.2 Outcomes (eg, date of occurrence, multiple event, severity measures related to event)?	☒	☐	☐	9.3
9.2.3 Covariates (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)?	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical Classification System)?	☐	☐	☒	N/A
9.3.2 Outcomes (eg, International Classification of Diseases-10, Medical Dictionary for Regulatory Activities)?	☒	☐	☐	9.3
9.3.3 Covariates?	☐	☐	☒	N/A
9.4 Is the linkage method between data sources described (eg, based on a unique identifier or other)?	☐	☐	☒	N/A

Comments:

This protocol describes the data sources as presented in registry protocols and publications. Information is not available for all items above.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☐	☒	☐	N/A
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☐	☐	☒	N/A
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	N/A
10.5 Does the plan describe methods for handling missing data?	☐	☐	☒	N/A
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

This protocol describes the analysis plan as presented in registry protocols and publications. Information is not available for all items above.

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

Comments:

This protocol describes the analysis plan as presented in registries protocols and publications. Information is not available for all items above.

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?	☐	☐	☒	N/A
12.1.2 Information biases?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)?	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility (eg, study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)?	☒	☐	☐	9.5

Comments:

This protocol describes limitations within the context of information provided in the registry protocols and publications.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	N/A
13.3 Have data protection requirements been described?	☒	☐	☐	9.6

Comments:

This protocol describes ethical issues within as presented in the registry contracts, protocols, and publications.

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

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
future amendments and deviations?				

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (eg, 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: 20 November 2017

Signature: PPD

Annex 2. BADBIR Company Report Template

1. Section 1 – Definitions and Notes

2. Section 2 – <*Biologic*> Patients
    - Demographics
    - Baseline Characteristics
    - Serious Adverse Events Reported Rates (example table provided)

3. Section 3 – Comparison Patients
    - Demographics
    - Baseline Characteristics
    - Serious Adverse Events Reported Rates (example table provided)

Example: Adverse Events Recorded (rates are per 1000 person-years)

Event	Males		Females		Total	
	Events	Rate (95% CI)	Events	Rate (95% CI)	Events	Rate (95% CI)
Total Serious Infection						
Pneumonia						
Septicemia						
Bone/Joint infection						
Opportunistic infection						
Other serious infection						
TB						
Respiratory (Non-Infection)						
Total Cardiac Disorders						
CHF (new or worsening)						
Myocardial infarction						
Other cardiac events						
CNS Disorders						
Demyelination						
Peripheral neuropathy						
Other CNS						
Skin (Non-Cancer)						
Total Hematologic Events						
Aplastic anemia						
Pancytopenia						
Agranulocytosis						
Other dyscrasia						

Event	Males		Females		Total	
	Events	Rate (95% CI)	Events	Rate (95% CI)	Events	Rate (95% CI)
Total Malignant Events						
Lymphoproliferative						
Lymphoma						
Myeloma						
Leukemia						
Other lymphoproliferative						
Skin cancer						
Non-melanoma skin cancer						
Melanoma						
Other skin cancer						
Other malignant solid tumors						
Other malignant SAE						
Pregnancy						
Death						

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