Janssen EMEA Medical Affairs*

Observational Study Protocol

An Observational Post-approval Safety Study of Golimumab in Treatment of Polyarticular Juvenile Idiopathic Arthritis (pJIA) Using the German Biologics JIA Registry (BiKeR)

Protocol PCSIMMA0237 AMENDMENT 5

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STUDY INFORMATION

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Name of Marketing Authorization Holder:	Janssen Biologics B.V.
Joint PASS:	No
Research question and objectives:	This PASS aims to monitor the safety of golimumab (GLM) use in the treatment of pJIA in regular clinical practice using the German Biologics JIA Registry (Biologika in der Kinderrheumatologie, BiKeR). The study comprises four study cohorts: a GLM cohort, a contemporary anti-tumor necrosis factor (anti-TNF) control cohort, a contemporary methotrexate (MTX) control cohort, and a historic anti-TNF control cohort for the final report. The primary objectives of the study are to describe the baseline clinical and demographic characteristics across study cohorts, to evaluate the risk of serious infections, malignancy, autoimmune processes, and pregnancy in patients treated with GLM and to compare the risks of these primary safety endpoints in the GLM cohort with those in the contemporary anti-TNF cohort (primary comparison) and with those in the contemporary MTX cohort (secondary comparison), adjusted for baseline characteristics.
Country of study:	Germany
Author:	PPD PhD Sr. Medical Advisor Post-marketing Commitments PPD

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Description of Abbreviated Term
ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse event
anti-TNF	anti-tumor necrosis factor
BiKeR	Biologika in der Kinderrheumatologie, BiKeR
cJADAS-10	Clinical Juvenile Arthritis Disease Activity Score based on a 10-joint count
CHAQ	Childhood Health Assessment Questionnaire
CI	confidence interval
CRF	case report form
CRP	C-reactive protein
DRFZ	Deusches Rheuma Forschungszentrum (German Rheumatism Research Center)
ESR	erythrocyte sedimentation rate
ETA	etanercept
EU	European Union
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GKJR	Gesellschaft für Kinder- und Jugendrheumatologie (German Society for Childhood Rheumatology)
GLM	golimumab
HLA	human leukocyte antigen
IBD	inflammatory bowel disease
ILAR	International League of Associations for Rheumatology
JADAS-10	Juvenile Arthritis Disease Activity Score based on a 10-joint count
JIA	juvenile idiopathic arthritis
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NSAID	nonsteroidal anti-inflammatory drug
PASS	post-authorization safety study
PedACR	American College of Rheumatology Pediatric response criteria
pJIA	polyarticular juvenile idiopathic arthritis
PY	person-year
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SLE	systemic lupus erythematosus
SPSS	Statistical Package for the Social Sciences
RMP	risk management plan
VAS	visual analogue scale

Definition of Terms

Registry	An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.
Study	The term “study” indicates the collection of data for research purposes only. The use of this term in no way implies that any treatments or procedures outside clinical practice, planned or otherwise, have been provided or performed.
Secondary use of data study	A study that has all information collected from source data or a retrospective database. Normally, there is no new collection of information from the patient, although this may be required to address specific questions. Studies/Programs/Related Research Activities with only one visit can be considered prospective or retrospective bearing in mind this definition and the source of information.

Post Authorization Safety Study (PASS)	Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

2. RESPONSIBLE PARTIES

Sponsor's Responsible Party	PPD PhD
Principal Participating Physician:	Dr Gerd Horneff, Professor
Sponsor's contact for this protocol:	PPD PhD
E-mail address or telephone number of contact person:	PPD

3. SYNOPSIS

Protocol Title: An Observational Post-approval Safety Study of Golimumab in Treatment of Polyarticular Juvenile Idiopathic Arthritis (pJIA) Using the German Biologics JIA Registry (BiKeR) (4.0, 14 March 2025)

Sponsor's Responsible Party: PPD Janssen EMEA Medical Affairs (Main Author)

NOTE: The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

Background and Rationale

SIMPONI® (golimumab [GLM]) received European marketing authorization for treatment of polyarticular juvenile idiopathic arthritis (pJIA) on 24 June 2016. In connection with this approval, the company is committed to conduct a post-authorization safety study (PASS) to monitor long-term safety of GLM in the treatment of pJIA in regular clinical practice setting.

The safety of GLM in treatment of pJIA was demonstrated in a double-blind, placebo-controlled, Phase 3, randomized-withdrawal trial. However, the long-term safety of GLM in this indication has not been characterized. Serious infections, malignancies, and autoimmune diseases have been reported with anti-tumor necrosis factor (anti-TNF) agents. This PASS is intended to monitor the safety of GLM use in treatment of pJIA in a post-marketing setting.

The BiKeR registry has been collecting data from patients with JIA treated with approved biologics in regular clinical practice since 2001. This registry is expected to include the majority of patients with pJIA treated with GLM in Germany. This PASS will use data collected in the BiKeR registry to monitor long-term safety and effectiveness of GLM in treatment of pJIA. To provide context for interpreting safety data, this PASS will also include data from contemporary patients with pJIA treated with alternative therapies, including other anti-TNF agents (adalimumab [ADA], etanercept [ETA], and their biosimilars when available) and methotrexate (MTX), as well as a historical anti-TNF cohort.

Research Question and Objectives

This observational PASS monitors the safety and effectiveness of GLM use in the treatment of pJIA in routine clinical practice using data from the German BiKeR registry. It uses a new user cohort design and comprises 4 study cohorts: GLM cohort, contemporary anti-TNF cohort (including ADA, ETA, or their biosimilars when available), contemporary MTX cohort, and historic anti-TNF cohort (ADA or ETA).

The objectives of this study are listed below.

Primary Objectives:

- To describe the baseline clinical and demographic characteristics of the GLM cohort, contemporary anti-TNF control cohort, contemporary MTX control cohort, and historic anti-TNF control cohort.
- To evaluate long-term safety of GLM in treatment of pJIA by describing the risks of the following primary safety endpoints for each of the 4 cohorts:
  - serious infections
  - malignancy
  - autoimmune processes
  - exposure during pregnancy

- To compare the risks of primary safety endpoints in the GLM cohort with those in the contemporary anti-TNF cohort (primary comparison); and with those in the contemporary MTX cohort (secondary comparison), adjusted for baseline characteristics.

Secondary Objectives:

- To describe incidence rates of the following secondary safety endpoints in the 4 study cohorts:
  - demyelinating disorders
  - serious depression including suicidality
- To describe the effectiveness (magnitude of treatment response) of the GLM by comparing disease activity measurements at Months 3, 6, 12, and 24 to baseline measurements among the GLM cohort.
- To describe the GLM treatment duration, discontinuation, and reasons for discontinuation.
- To describe the course of growth and development among the GLM cohort.

Exploratory Objective:

- Among the GLM initiators who achieve remission and then discontinue GLM, describe the disease course after the GLM discontinuation.

Study Design

This is a long-term observational cohort study to monitor safety and effectiveness of GLM in the treatment of pJIA using data prospectively collected in the BiKeR registry. It will use a new user cohort design and comprise 4 study cohorts:

- GLM cohort: patients with pJIA who are first- time users of GLM.
- Contemporary anti-TNF control cohort: a pooled cohort of patients with pJIA who are first-time users of other anti-TNF agents (ETA, ADA, or their biosimilars). This cohort will be enrolled concurrently with the GLM cohort and serve as the primary comparison for safety outcomes.
- Contemporary MTX control cohort: a cohort of patients with pJIA who are first-time users of MTX will be enrolled concurrently with the GLM patients. This cohort will serve as a secondary comparison for safety outcomes.
- Historic anti-TNF control cohort: to provide additional context for safety outcomes, a large historic cohort of patients with pJIA who were first-time users of ETA or ADA will be extracted from the BiKeR database. This cohort is to provide more stable incidence rates as a reference for safety outcomes.

Patients in the contemporary cohorts will be enrolled into the registry at the time of initiation of cohort-defining therapies and will be followed at Months 3, 6, and every 6 months, thereafter up to 5 years regardless of treatment discontinuation or switch. The BiKeR registry uses structured case report forms (CRF) to systematically collect data at each visit. Patients in the historic anti-TNF cohort were enrolled into the BiKeR registry prior to start of this PASS and were followed-up with the same frequency.

Setting and Study Population

The study population will comprise contemporary patients with pJIA who newly initiated therapy with GLM, other anti-TNFs, or MTX and who are enrolled in the German BiKeR registry. In addition, it will include a historic cohort of anti-TNF patients extracted from the BiKeR database.

Variables

All variables relevant for this PASS will be extracted from the BiKeR registry.

Exposures:

The main exposures of interest are GLM and other anti-TNFs in the treatment of pJIA. The additional exposure of interest is MTX.

Safety outcomes:

Adverse events (AEs) are recorded during patient follow up within the BiKeR registry.

The primary safety outcomes comprise the following adverse events:

- serious infections
- malignancy
- autoimmune processes
- exposure during pregnancy

The secondary safety outcomes are:

- demyelinating disorders
- serious depression including suicidality

Effectiveness outcomes:

Effectiveness is prospectively measured in BiKeR using the American College of Rheumatology Pediatric response criteria (PedACR), the Juvenile Arthritis Disease Activity Score based on a 10-joint count (JADAS-10 and clinical JADAS-10 [cJADAS-10]) and the modified ACR criteria for inactive disease on medication.

For GLM patients, the proportion of patients achieving a PedACR 30, 50, 70, and 90 response, the proportion of patients with no/minimal/moderate/high disease activity, based on JADAS-10/cJADAS-10 (using the 2012-2014 and 2021 cut-offs, respectively) and the proportion of patients with ACR-defined inactive disease at Months 3, 6, 12, and 24 will be extracted from the registry.

Drug discontinuation**:**

For the GLM cohort, number of patients who discontinue GLM, reasons for discontinuation and the duration from initiation to discontinuation will be extracted from the BiKeR registry. For patients who discontinue GLM after remission, time to disease flare and retreatment will be extracted.

Growth and development:

For the GLM cohort, data on height and weight at baseline and every 6 months, thereafter during treatment will be extracted from the BiKeR registry.

Covariates:

The following covariates are collected in the BiKeR registry at cohort entry and will be extracted for all cohorts:

- age
- sex
- race/ethnicity
- duration of disease since diagnosis

- baseline disease severity
- comorbidity
- history of treatments with biologics
- co-medications

Data Sources

All data will be obtained from the German BiKeR registry database.

Study Size

This PASS will include all eligible patients with pJIA in Germany who newly initiated GLM and who are enrolled in the BiKeR registry. It is anticipated that the registry will enroll about 200 GLM-exposed patients during the study. The actual study size will depend on market uptake of GLM for the treatment of pJIA in Germany. Similarly, the study will include about 400 contemporary initiators of other anti-TNFs, and up to 500 contemporary initiators of MTX. In addition, a historic anti-TNF cohort of 2,158 patients will be extracted from the BiKeR database.

Data Analysis

Descriptive analysis:

Basic descriptive tabulations and statistical analyses will be performed.

- Patient clinical and demographic characteristics at baseline will be described for each cohort.
- For each primary safety endpoint, number of events and incidence rate will be calculated for each cohort. Subgroup analyses stratified by history of prior anti-TNF use will be conducted if data permit.
- For each secondary safety endpoint, the number of events and incidence rate will be calculated for the GLM cohort, and 2 contemporary comparator cohorts. For the historic anti-TNF cohort, frequencies and incidence rates will be calculated only for those secondary endpoints that had been systematically collected on the registry CRF during the historic observation period.
- For the GLM cohort, magnitude of treatment response (the proportion of patients achieving a PedACR 30, 50, 70, and 90 response, the proportion of patients with no/minimal/moderate/high disease activity, based on JADAS-10/cJADAS-10 (using the 2012-2014 and 2021 cut-offs, respectively, as well as the proportion of patients with ACR-defined inactive disease) will be described by comparing disease activity measurements at Months 3, 6, 12, and 24 to baseline measurements.
- For the GLM cohort, treatment duration and reasons for GLM discontinuation will be described. For patients who discontinue GLM after remission, time to disease flare and retreatment will be described.

Comparative analysis:

If data permit, comparative analyses will be conducted for primary safety outcomes. Multivariate models will be used to estimate the risks by comparing the GLM cohort to contemporary comparator cohorts adjusting for potential covariates.

Milestones

Milestone	Planned Date
Start of data collection	January 2018
End of data collection	December 2026
Registration in the EU PAS register	January 2018
Study progress reports	First report, December 2018; periodically thereafter
Final report of study results	June 2027

4. AMENDMENTS AND UPDATES

Amendment in Protocol Version 4.0 (2025): The protocol was amended to reflect the change in sponsorship from Merck to Janssen EMEA Medical Affairs and adapted to the Janssen template; the cJADAS-10 score and the 2021 JADAS-10/cJADAS-10 cutoff criteria for disease activity were added. The contractor for the statistical analyses was changed and JIA subtypes were removed as potential confounders for serious infections.

Amendment in Protocol Version 3.0 (2023): The protocol was amended to extend the end of enrollment period from 23 June 2021 to 23 June 2026 to reach target of 200 GLM patients.

Updates in Protocol Version 2.2 (2022): Administrative in nature. The protocol was amended to incorporate updated MAH contact and to reflect changes in submission frequency of progress reports.

Updates in Protocol Version 2.1 (2022): Administrative in nature to encompass sponsor's business name change.

Amendments in Protocol Version 2.0 (2020): The secondary objectives are aligned with safety concerns in the Simponi EU RMP. The protocol was amended to remove all safety concerns listed as secondary objectives that are no longer included in the list of safety concerns in the current EU RMP of Simponi (version 21.1).

More specifically, the secondary outcomes of Congestive heart failure, Hypertension, Serious hepatotoxicity, Vasculitis, Hematologic reactions, Serious systemic hypersensitivity (including anaphylactic reaction), Serum sickness, Hepatitis B virus reactivation, Maladministration/administration error, Medication error (wrong dose related to different strengths), psoriasis (new onset or worsening of pre-existing) and Sarcoidosis/sarcoid-like reaction are removed.

The primary outcomes are retained.

The table below summarizes the main changes to the protocol.

Number	Date	Section of Protocol	Amendment or Update	Reason
1	25 Sep 2020	PASS information, 2, 4, 5.1, 5.2, 6, 6.1, 6.2, 7.3.2.1, 7.3.2.2, Annex	Amendment	To reflect administrative changes, and protocol changes in rationale/background, objectives and outcomes to be aligned with EU-RMP (version 21.1) and EU SmPC, and to add MedDRA terms table.
2	29 Jun 2022	1	Update	To reflect administrative changes.
3	18 Nov 2022	PASS information, 2, 4	Amendment	To reflect administrative changes and changes in submission frequency of progress reports.
4	10 May 2023	7.2.3	Amendment	To reach target of 200 GLM patients, the end of enrollment period extended from 23 June 2021 to 23 June 2026 to allow 6 months follow-up for the last patient enrolled before the end of data collection in December 2026.
5	14 March 2025	Throughout the protocol Marketing Authorization Holder Page 3 8.3.3.3 8.3.3.3 8.3.4.1 8.7.2.2 8.7.3 8.9 10	Amendment	To transfer the protocol to the Janssen template for non-interventional studies with secondary data collection. To reflect change in the MAH contact details. To reflect the change in sponsorship from Merck to Janssen. To reflect the addition of the clinical JADAS-10 score (without ESR). To reflect the addition of the JADAS-10 and cJADAS-10 cut-off criteria for disease activity which were updated in 2021. Removal of JIA subtypes as confounders for serious infections. To change the contractor for the statistical analyses. To allow for different matching method in final report. To add strengths of the research methods. To reflect the change in the collection of AEs to secondary data collection with no access to patient level data.

5. MILESTONES

The planned dates for key milestones in this study are outlined in Table 1.

Table 1: Study Milestones

Milestone	Planned Date
Start of data collection	January 2018
End of data collection	December 2026
Registration in the EU PAS register	January 2018
Study progress reports	First report, December 2018; periodically thereafter
Final report of study results	June 2027

6. RATIONALE AND BACKGROUND

6.1. Background

Juvenile idiopathic arthritis is the most common chronic inflammatory disease in children and can lead to severe disability (Minden 2000; Petty 1999; Woo 1998). The term JIA encompasses a group of clinically heterogeneous arthritides that begin prior to age of 16 years, are of unknown causes and present with joint pain, stiffness, and swelling that persist for longer than 6 weeks. The incidence in Caucasian children <16 years has been reported to be 19.8/100,000 children (Danner 2006). According to the International League of Associations for Rheumatology (ILAR) classification, JIA is sub-classified into 7 distinct categories (Petty 2004). Treatment strategies are guided by sub-classification, since outcome and type, and rate of complications among these JIA classes are different. Conventional therapy with MTX, leflunomide, or sulfasalazine is often not successful in ameliorating disease especially in patients with polyarticular and systemic subtypes (Minden 2000). The only randomized study with 2 active comparators showed that about 50% of the clinical disease activity persists despite prolonged therapy (Silverman 2005). This warrants more efficient treatment for those patients who do not reach remission.

Anti-TNF therapy, as a biologic treatment option, has been shown to be successful in treatment of patients with JIA. Since anti-TNF agents are routinely used in the treatment of patients with JIA, remission of JIA has become a goal well in reach. Golimumab is a newer anti-TNF agent that was approved, in combination with MTX, in the EU on 24 June 2016 for treatment of pediatric patients with pJIA (with a body weight of ≥40 kg) who have inadequately responded to previous therapy with MTX. Since 18 February 2019, the pJIA indication for GLM has been expanded to include a new pediatric presentation of GLM 45 mg/0.45 mL, allowing children of 2 years of age and older with a body weight of <40 kg (who need a dose <50 mg) to be treated with GLM solution for injection.

The BiKeR registry has been set up since 2001 and has a proven record of studying safety and effectiveness of biologic treatments in JIA (Horneff 2011; Horneff 2004; German Biologics JIA Registry; Klotsche 2016; Schmeling 2014). It has captured the majority of patients with pJIA who are receiving biologic therapies in Germany. This observational PASS will use data collected in the German BiKeR registry to evaluate long-term safety of GLM in the treatment of pJIA compared with treatments with other anti-TNF agents and MTX monotherapy.

6.2. Overall Rationale for the Study

Golimumab is an anti-TNF agent, was first approved on 01 October 2009 in the European Union for the indications of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. On 19 September 2013, use of GLM was approved to treat ulcerative colitis. On 22 June 2015, use of GLM was approved to treat non-radiographic axial spondyloarthritis. Golimumab received European marketing authorization for the treatment of pediatric patients with pJIA on 24 June 2016 (see Section 6.1 for details). In connection with the approval in this indication, the sponsor is committed to conduct a required PASS to monitor long-term safety of GLM in the treatment of pJIA in regular clinical practice setting. This PASS will use data from the German

Biologics JIA Registry (Biologika in der Kinderrheumatologie, BiKeR) to fulfill this regulatory commitment.

Golimumab has been proven to be safe and effective in treatment of adult MTX-refractory rheumatoid arthritis in several studies (Kay 2008; Keystone 2010; Keystone 2009; Smolen 2012). Golimumab was also studied in children with pJIA in a double-blind, placebo-controlled, Phase 3 randomized-withdrawal trial, and its safety was demonstrated (Brunner 2014). However, the long-term safety of GLM in this indication has not been characterized. Serious infections, malignancies, and autoimmune diseases have been reported in patients under therapy with anti-TNF agents. This PASS is intended to monitor the safety of GLM use in the treatment of patients with pJIA over a long time period in a post-marketing setting.

The German BiKeR registry is a non-interventional, observational registry that has been collecting data from patients with JIA treated with approved biologic therapies in regular clinical practice since 2001. Patients are followed from enrollment in the registry until they leave the care of the pediatric rheumatologists, which generally occurs around their eighteenth birthday. Altogether, more than 13,000 observation years have been accrued and data concerning effectiveness and safety of biologic agents have been collected. This registry supports safety investigation of these biologic drugs in routine clinical care over a long period of time (Klotsche 2016).

This PASS will use data collected as part of the ongoing BiKeR registry in Germany to monitor long-term safety and effectiveness of GLM in the treatment of pJIA in regular clinical practice. This registry is expected to capture the majority of GLM treatments used for pJIA in Germany. To provide context for interpreting safety data of patients with pJIA treated with GLM, this PASS will also include patients with pJIA treated with other therapies, including other anti-TNF agents, ie, ADA, ETA and their biosimilars (when available in the future), and MTX.

7. RESEARCH QUESTION AND OBJECTIVES

Research Question

This observational PASS monitors the safety and effectiveness of GLM use in the treatment of pJIA in routine clinical practice using data from the German BiKeR registry. It uses a new user cohort design and comprises 4 study cohorts: GLM cohort, contemporary anti-TNF cohort (including ADA, ETA, or their biosimilars when available), contemporary MTX cohort, and historic anti-TNF cohort (ADA or ETA).

Objectives and Outcomes/Measures of Interest

In this PASS, no prior research hypotheses have been formulated.

The primary objectives are:

- To describe the baseline clinical and demographic characteristics of the 4 study cohorts.
- To evaluate long-term safety of GLM in treatment of pJIA by describing the risks of the following primary safety endpoints for each of the 4 cohorts.

  - serious infections (including opportunistic infections, tuberculosis and hepatitis B reactivation)
  - malignancy
  - autoimmune processes (including thyroiditis, autoimmune diabetes, uveitis, psoriasis, IBD, celiac disease, demyelinating disorders as well as SLE)
  - exposure during pregnancy
- To compare the risks of primary safety endpoints in the GLM cohort with those in the contemporary anti-TNF cohort (primary comparison); and with those in the contemporary MTX cohort (secondary comparison), adjusted for baseline characteristics.

The secondary objectives are:

- To describe incidence rates of the following secondary safety endpoints in the 4 study cohorts: demyelinating disorders and serious depression including suicidality.
- To describe the effectiveness (magnitude of treatment response) of GLM by comparing disease activity measurements at Months 3, 6, 12, and 24 to baseline measurements among the GLM cohort.
- To describe GLM treatment duration, discontinuation and reasons for discontinuation.
- To describe the course of growth and development among the GLM cohort.

The exploratory objective is:

- Among GLM initiators who achieve remission and then discontinue GLM, describe the disease course after GLM discontinuation.

Refer to Section 8.7 for statistical aspects of outcomes or measures of interest.

8. RESEARCH METHODS

8.1. Study Design

This is a long-term, observational cohort study using prospectively collected data from the BiKeR registry to monitor safety and effectiveness of GLM in treatment of pJIA in regular clinical practice. It will use a new user cohort design and comprise 4 cohorts: GLM cohort, contemporary anti-TNF control cohort, contemporary MTX control cohort and historic anti-TNF control cohort. All patients are followed in the same manner in the BiKeR registry for evaluation of study outcomes.

The study period will range from January 2018 (start of data collection) to December 2026 (end of data collection). The details of study periods and dates are provided in Section 5.

In this study, data collected will be de-identified data drawn from the BiKeR registry database. Further details of data sources are provided in Section 8.4.

8.1.1. The German BiKeR Registry

The German BiKeR registry is a longitudinal multicenter observational registry that is an initiative of the Centre for Pediatric Rheumatology Sankt Augustin supported by the German Society for Childhood Rheumatology (Gesellschaft für Kinder- und Jugendrheumatologie [GKJR]). The registry was set up by pediatric rheumatologists in Germany to prospectively monitor the long-term safety and effectiveness of biologics in treatment of JIA (Horneff 2004). All participating physicians are board-certified pediatric rheumatologists. The BiKeR registry includes about 80 study sites and since its inception has followed more than 4,000 patients in Germany and Austria (For the purpose of this PASS, only German sites will be included because very few patients have been enrolled from Austria). The BiKeR registry includes pediatric patients, aged 2 to 18 years, who meet ILAR criteria for JIA (Petty 2004) when they initiate biologic therapy or MTX. However, the registry excludes patients who are pregnant at the time of registry entry or have contraindications to registry-qualifying treatments that are listed in the German product information. The BiKeR patient population is generally comparable to other MTX- and biologic-eligible JIA populations in EU countries in terms of age of onset, age of starting treatment, sex, JIA subcategory distribution, history of uveitis, HLA B27 positivity, pretreatment and co-treatment with steroids, and MTX (Anink 2013; Kearsley-Fleet 2016; Southwood 2011; Tarkiainen 2015). It thus appears that the BiKeR population is representative of the EU JIA population.

The BiKeR registry began in 2001 and over time, newly approved biologics have been added as exposures of interest. Data from the BiKeR registry have been used to perform post-marketing safety studies for ETA, ADA, and other biologics. (Klotsche 2016; Schmeling 2014)

Patient demographic characteristics, disease history, and previous treatments are documented at the time of patient enrollment. Details about relevant treatment and reasons for discontinuation, concomitant therapy, disease activity, and data on AEs are prospectively collected using standard CRFs at the start of treatment, at Months 3 and 6, and every 6 months thereafter (Horneff 2004). These follow-up intervals represent intervals from routine clinical care and are sufficient to monitor the effects of the drugs, even if the response is not immediate. Patients are followed from enrollment in the registry until they transfer out of pediatric rheumatology practices upon reaching adulthood around their eighteenth birthday.

Over time, BiKeR CRFs have been updated to reflect concerns about new potential risks for biologic agents. The registry CRF includes a list of AEs of interest. This list has been expanded to include additional AE terms (such as, hematologic reactions, serum sickness, hepatitis B virus reactivation, serious depression including suicidality, maladministration/administration error, and sarcoidosis/sarcoid-like reaction) to systematically collect information on these events. The updated CRF has been used across the BiKeR registry at each visit. In addition to pre-specified AEs of interest, treating physicians are able to report other AEs that may arise during follow-up.

BiKeR operational procedures

The BiKeR registry collects data during routine clinical care of patients with JIA. Treating physicians make decisions regarding clinical investigations, interventions or treatments which are not influenced by the registry. No other investigations or measures or additional visits other than what would be needed in routine clinical care are conducted for the BiKeR registry.

The BiKeR registry follows a standard procedure at all participating centers. Physicians are provided with a registry kit that includes the registry study protocol, structured CRFs including parental informed consent and patient assent forms, AE reporting form, SAE and pregnancy forms, and drug discontinuation forms. Patients are evaluated at enrollment after the informed consent is signed and at Months 3 and 6, and every 6 months thereafter by treating physicians.

At the enrollment visit (baseline), treating physician examines the health status of patient at his/her office and completes the baseline CRF. The diagnosis, date of symptom onset, any past treatments, global assessment of current disease activity, 72-joint count, and the details of current biologic and non-biologic medication use are recorded on the CRF.

The patient is prospectively monitored via regular scheduled visits in usual clinical practice. At each visit, the physician examines the patient and decides with the patient regarding treatment changes. The relevant information closest to the registry scheduled visit date will be used. The follow-up CRFs include current disease activity, the date and reasons for change of medications, if applicable, as well as occurrence of AEs.

All CRFs filled out by patient/parent and by treating physician are sent to the registry coordinating center by mail or fax. Data administration is handled by trained personnel in the coordinating center. All documents are double checked for completeness and accuracy. Queries are sent in case of missing information or inconsistencies. The participating centers are monitored by trained personnel in regular intervals.

BiKeR data management and quality control

The BiKeR registry supplies paper CRFs to the participating study centers. CRFs must be completed for each patient enrolled in this registry. All CRFs must be legible and completed in indelible ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision, and must be initialed and dated by the investigator or his/her designee. Data are not to be obliterated by blacking out, correction fluid, or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (eg, transcription error) should accompany the change. The original of the CRFs is sent to the BiKeR registry by post and a copy remains with the investigator.

All paper CRF data are double entered by the BiKeR staff. All original forms are stored. Each form is scanned as a pdf file, which is placed on a secured server. Security and backups are under the responsibility of the IT department of Asklepios Gesellschaft mit beschraenkter Haftung (limited company).

Data are coded in a standard way for input into the database. For example, sex is coded as: 1=male, 2=female; JIA subcategories are recorded as numbers from 1 to 7; Medications (active ingredient) have a numerical code; Dates (date of birth, disease onset) are recorded in date format; Absolute values are recorded for disease activity parameters (number of active joints, JADAS, VAS). Comorbidities and AE are coded according to MedDRA coding system and each AE receives a coded number. Data are entered into a Microsoft Access database and transferred to Statistical Package for the Social Sciences (SPSS, IBM Software) database for statistical analysis.

Quality control is performed in multiple steps. Plausibility checks are done at data input, data transfer, and at regular intervals through automated programs.

BiKeR informed consent

Written informed consent is collected at enrollment into the BiKeR registry according to the Declaration of Helsinki requirements (WMA Declaration of Helsinki). The BiKeR registry investigators or representatives explain the nature of the BiKeR registry to the parents or legal guardians and the patient, and answer all questions regarding this registry. Prior to inclusion in the BiKeR registry and any registry-related documentation being undertaken on the patient, the informed consent statement must be reviewed, signed and dated by the parents or legal guardians and the person who administers the informed consent. Children greater than 12 years are to sign the patient information as well. A copy of the signed informed consent is given to the parents or legal guardians and the original is placed in the patient's medical record. An entry must also be made in the patient's dated source documents to confirm that informed consent is obtained prior to any registry-related documentation and that the patient has received a copy.

BiKeR receives data from the participating centers only in pseudonymized format (ie, identity is encoded). Only the treating medical staff in the centers can identify the patient. On-site monitoring is done by trained BiKeR staff who adhere strictly to data security and patient confidentiality regulations. The BiKeR registry follows GCP. The registry is approved by the Ethics Committee of the Medical Faculty of the Martin-Luther University Halle-Wittenberg, Halle, Germany, and by the Ethics Committee of the Aerztekammer Nordrhein, Dusseldorf, Germany. The BiKeR registry protocol, any protocol amendments, the informed consent, and all other forms of patient information related to the registry (eg, advertisements used to recruit patients) and any other necessary documents have been reviewed by the Independent Ethics Committee.

8.2. Setting and Study Population

8.2.1. Study Setting

Data will be drawn from the BiKeR registry database. Further details of data sources are provided in Section 8.1. The BiKeR registry includes about 80 study sites and since its inception has followed more than 4,000 patients in Germany and Austria (For the purpose of this PASS, only German sites will be included because very few patients have been enrolled from Austria).

8.2.2. Patient Selection Criteria

The population for this PASS will be drawn from the BiKeR registry in Germany and will include contemporary male and female pediatric patients of any race or ethnicity with an active disease of pJIA who newly initiate therapy with GLM, other anti-TNFs (ADA, ETA, or their biosimilars when available), or MTX. The enrollment date is defined operationally as the date of initiation of the cohort-defining drug. In addition, to provide additional context for the safety outcomes, a large historic anti-TNF cohort of ETA and ADA patients with pJIA will be drawn from the BiKeR registry database to provide more stable incidence rates of safety outcomes as a reference.

The specific definitions of the 4 study cohorts are as follows:

- GLM cohort: Patients with pJIA who are newly treated with GLM and who are enrolled in the BiKeR registry. Patients can receive MTX before, during or after GLM treatment; they can also have other anti-TNFs before or after GLM treatment.
- Contemporary anti-TNF control cohort: A pooled cohort of patients with pJIA who are newly treated with other anti-TNF agents (ETA, ADA, or their biosimilars) and who are enrolled in the BiKeR registry. The anti-TNF agent can be the first or subsequent treatment. The patient can receive MTX before, during or after anti-TNF treatment. This cohort will be frequency matched by body weight to the GLM cohort and serve as the primary comparison group for safety outcomes.
- Contemporary MTX control cohort: A cohort of patients with pJIA who are newly treated with MTX and who are enrolled in the BiKeR registry. The patient is naïve to all biologic agents before initiation of MTX. Patients of this cohort may start an anti-TNF agent later on. Those patients will remain in the MTX exposure cohort until start of an anti-TNF agent and from that point of time will be followed in the GLM cohort or the contemporary anti-TNF exposure cohort, as appropriate. This cohort will be frequency matched by body weight to the GLM cohort and serve as the secondary comparison group for safety outcomes.
- Historic anti-TNF control cohort: A historic cohort of patients with pJIA who were enrolled in the BiKeR registry for first time use of ETA or ADA between 24 June 2006 and 23 June 2016. It can be the first or subsequent anti-TNF agent for the treatment of pJIA. The patient can receive MTX before, during or after anti-TNF treatment. This large historic cohort will provide stable reference rates for safety outcomes. Cohort membership is not exclusive; patients may enter the PASS on 1 cohort and switch cohorts if treatment changes occur during follow-up.

8.2.2.1. Inclusion Criteria

To enter this PASS, patients need to meet the following inclusion criteria.

For the contemporary cohorts:

- Patients with pJIA who are newly started with anti-TNFs (GLM, ETA, ADA, or their biosimilars) or MTX and who are enrolled in the BiKeR registry between 24 June 2016 and 23 June 2026.

For the historic anti-TNF cohort:

- Patients with pJIA who were enrolled in the BiKeR registry for first time use of ETA or ADA between 24 June 2006 and 23 June 2016.

8.2.2.2. Exclusion Criteria

In addition to the general BiKeR exclusion criteria described in Section 8.1.1, for this PASS, patients with a history of malignancy at the time of cohort entry are excluded.

8.2.3. Duration of Study Period(s) and Follow-Up

Patient Follow-up

For this PASS, patient overall follow-up time is the time from date of cohort entry until the date of end of follow-up. Date of cohort entry corresponds to the date of first initiation with one of the cohort-defining medications.

In the analysis for each outcome, the date of end of follow-up will be defined as the earliest of the following events: occurrence of study outcome of interest, withdrawal or transfer out of the registry upon reaching adulthood, loss to follow-up, death, or end of study period, whichever comes first.

Loss to follow-up definition: Clinical expectations are that patients receiving anti-TNFs or immunomodulatory therapies have regular follow-up visits with treating physicians at least every 6 months. Patients who have received these agents but have no recorded follow-up visit with treating physicians for at least 13 months after last clinical contact will be defined as lost to follow-up.

In the clinical care of patients with pJIA, therapies could change over time. Stopping or switching therapy will not terminate follow-up. Patients will be continuously followed and monitored for up to 5 years after initial inclusion in this PASS or until end of follow-up, whichever comes first.

A patient's baseline data will be collected, where available, after the day consent was signed.

The exposure date is defined as the date of the treatment initiation. The decision to start treatment was taken per clinical practice and prior to enrollment and is not to be influenced by a patient's participation in this study.

The data collection period will document data available from time of consent until the prespecified data cutoff (progress report) or the end of data collection for this study (final study report).

8.2.3.1. Definition of Risk Windows

Because there are various possible effects on different study outcomes after drug discontinuation, the risk window for monitoring different study outcomes will differ. In the primary analysis, one definition of risk window for malignancy and another for non-malignancy safety outcomes (Section 14.1) will be used for this PASS, which are commonly used in monitoring the safety of

biologic agents in rheumatologic research (Dixon 2007; Klotsche 2016). A variety of sensitivity analyses using different modified risk windows will also be conducted in the final analyses.

For malignancy outcomes: The potential drug effect on risk of neoplastic outcomes may persist after discontinuation of an anti-TNF agent, the primary risk window for anti-TNF exposures is defined as "once exposed, always at risk", as has been the regular practice in studies of risk of cancer associated with anti-TNF agents.

- For GLM and other anti-TNFs exposure, the risk window begins with the initiation of the agent and extends until end of follow-up regardless of drug discontinuation or switching. If patients switch from 1 anti-TNF to another anti-TNF agent, subsequent follow-up person-years (PY) and events will be attributed to both agents.
- For MTX exposure: the risk window begins at the start of MTX until end of follow-up or at time of switching to or adding an anti-TNF agent, whichever occurs first.

In addition, alternative definitions of the risk window will be included as sensitivity analyses for malignancies in the final analyses. These analyses will lag the start of time at risk and vary the potential period at risk after discontinuation of exposure:

- Alternative scenario 1: For all study exposures, the risk window begins 6 months after start of current exposure and extends until end of follow-up, regardless of drug discontinuation or switching. In case of a switch from agent A to agent B, an event occurring within 6 months after the switch will be attributed to agent A only; an event occurring beyond 6 months will be attributed to both agents.
- Alternative scenario 2: For all study exposures, the risk window begins 6 months after start of current exposure and ends 2 years after discontinuation of exposure or at the end of follow-up whichever occurs first. In case of a switch, event attribution will be same as scenario 1.

For all other safety outcomes: The primary risk window for all other safety outcomes for all exposures of interest (including GLM, other anti-TNFs, and MTX) begins with initiation of the agent and extends through 90 days after the last treatment, or until end of follow-up, whichever comes first. In the case of a switch from agent A to agent B, the risk windows for the 2 agents can overlap, in which case the event will be attributed to both agents. In addition, we will conduct sensitivity analyses shortening the extension window to 30 days after drug switching (Curtis 2011; Grijalva 2011; Yun 2015).

The final analysis will also explore use of an alternative approach to account for non-malignancy outcomes that occur around the time of switching therapies. An indicator for therapy initiation in the context of a switch will be flagged for the first 90 days into a new course of therapy that immediately follows treatment with another JIA therapy. Using this approach, one should be able to generate separate risk estimates associated with ongoing therapy with GLM (or a comparator) and also in the context of a recent switch, when clinical circumstances prompting the change in therapy may actually be important determinants of short-term risk of the safety outcome, independent of the new therapy. This approach will be explained in greater detail in the SAP.

8.3. Variables

8.3.1. Baseline Information

Information on demographics, pre-treatment, concomitant treatment, clinical characteristics, and disease activity parameters and adverse events is prospectively documented in the BiKeR registry at baseline and at follow-up visits. Data on all enrolled patients are collected in the same way regardless of their therapies.

For this PASS, the following relevant variables will be obtained from the BiKeR registry.

8.3.2. Exposure

The main exposures of interest are treatment with GLM and other anti-TNFs (ETA, ADA, or their biosimilars). The additional exposure of interest is treatment with MTX. Information on treatment exposure is recorded prospectively by treating physician on the BiKeR CRFs at baseline and at each follow-up visit, including the start date and, if relevant, the end date of the administration of the medication, possible changes in the dosage and their causes since the last visit.

Four study cohorts are formed based on treatment exposure. Only first time use of an anti-TNF or MTX during the study period will qualify for cohort entry. Prevalent use of a study medication will not qualify. A patient switching from one anti-TNF agent to another will, however, qualify for cohort entry. See Section 8.2.2 for more information.

8.3.3. Outcomes

8.3.3.1. Primary Safety Outcomes

For this PASS, the primary safety outcomes (Section 14.1) comprise the following incident adverse events occurring during follow-up after drug exposure:

- serious infections (including opportunistic infections, tuberculosis, and hepatitis B virus reactivation)
- malignancy
- autoimmune processes (including thyroiditis, autoimmune diabetes, uveitis, psoriasis, IBD, celiac disease, demyelinating disorders, as well as SLE)
- exposure during pregnancy

This PASS relies on secondary use of data collected by the BiKeR registry and thus relies on the case definitions used by the registry. Note that the registry does not perform any adjudication of endpoints; diagnoses reported by treating physicians are accepted at face value.

The BiKeR registry defines a serious infection as an infection that fulfills the SAE definition (death, a life-threatening event, hospitalization [initial or prolonged], disability or permanent damage, a congenital anomaly/birth defect, or required intervention to prevent permanent impairment or damage) or important medical event that may jeopardize the patient and may require medical/surgical intervention to prevent other outcomes. Opportunistic infection is defined as an

infection by a microorganism that normally does not cause disease but does so when lowered resistance to infection is caused by the impairment of the body's immune system (Winthrop 2015). Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis.

Malignancy is defined as diseases in which abnormal cells divide without control and can invade nearby tissues. Malignancies can affect every location, organ or organ systems in the body. Malignancy is diagnosed by treating physicians in clinical practice and recorded in the BiKeR registry. Confirmation of diagnosis with pathology reports are requested if available.

Autoimmune processes are a collection of conditions arising from an abnormal immune reaction produced by an individual's white blood cells or antibodies acting on the body's own tissues or extracellular proteins. There are multiple types of autoimmune diseases with different clinical presentations. Typical autoimmune diseases occurring in association with JIA include thyroiditis, autoimmune diabetes, uveitis, psoriasis, chronic IBD, celiac disease, as well as demyelinating disorders. In clinical practice autoimmune diseases are diagnosed by treating physicians according to clinical presentation/criteria and are accepted at face value by BiKeR where no additional reclassification occurs at the registry.

All information on the primary safety outcomes will be extracted from the BiKeR registry database. In the registry, all safety outcomes are prospectively ascertained using the standard CRF forms completed by the treating physician at each visit. The CRF forms, including detailed AE forms of special interest are used to document the occurrence of AEs at the time the AE comes to the knowledge of the treating physician, or at least at scheduled visit. Reported SAEs and AEs of special interest are tracked until the final outcome has been reported. (Schmeling 2014)

Any pregnancy that occurs after treatment initiation up to 180 days after the last treatment with the medication is identified by the treating physician and pregnancy outcomes are documented using the standard pregnancy form in the BiKeR registry. The form includes information on premature pregnancy termination (miscarriage or abortion), mode of delivery, maternal complications, and outcomes of the baby around time of delivery (such as stillbirth, live birth, low birth weight, and malformation).

8.3.3.2. Secondary Safety Outcomes

The secondary safety outcomes (Section 14.1) for this PASS are additional risks to be monitored for GLM. They include the following incident adverse events which occur during follow-up after drug exposure:

- demyelinating disorders
- serious depression including suicidality

All information on secondary safety outcomes will be extracted from the BiKeR registry.

8.3.3.3. Effectiveness Outcomes

In the BiKeR registry, effectiveness (clinical improvement in disease activity) is prospectively measured and determined using the American College of Rheumatology (ACR) PedACR

(Giannini 1997), JADAS-10 (Consolaro 2009), and cJADAS-10 (McErlane 2013), and the ACR-defined criteria for inactive disease on medication (Wallace 2011).

To assess the activity of arthritis, at each routine visit patients or parents are asked to report disease activity, physical examination including clinical investigations is performed, and the joints of the patient are examined for pain, swelling, and limited movement.

In this PASS specifically for the GLM treated patients, effectiveness data of GLM treatment at Months 3, 6, 12, and 24 by comparison to baseline disease activity measurements will be extracted from the BiKeR registry database, which will include the following parameters:

- PedACR 30, 50, 70, and 90 scores: Clinical improvement (30%, 50%, 70%, and 90%) in disease activity is prospectively measured using the PedACR criteria (Giannini 1997). PedACR 30 is defined as a 30% improvement in at least 3 out of 6 PedACR core parameters compared to baseline without deterioration of more than 30% in more than 1 of the remaining items; PedACR 50 is defined as a 50% improvement in 3 out of 6 PedACR core parameters compared to baseline without deterioration of more than 30% in more than 1 of the remaining items; similar definitions apply for PedACR 70 and 90. The number and proportion of patients with PedACR 30, 50, 70, and 90 response will be determined.
- JADAS-10 and cJADAS-10 scores: The original JADAS-10 includes the following disease activity measures: physician's global assessment, parent global assessment of well-being, the ESR and a count of 10 joints with active disease (any involved joint, irrespective of its type); the cJADAS-10 is a clinical 3-component version of the original score, which excludes the ESR (Consolaro 2009; McErlane 2013). The number and proportion of patients reaching the state of JADAS-remission, JADAS-minimal disease activity and JADAS acceptable disease activity will be determined. In 2021, new JADAS-10 cutoff and cJADAS-10 (clinical JADAS-10) cutoff criteria were introduced to determine patients' disease activity states (Trincianti 2021). The new JADAS-10 and cJADAS-10 criteria are added to the study in addition to the previously used JADAS-10 cutoff criteria (2012-2014) (Consolaro 2012). Disease activity states based on the JADAS-10 and cJADAS-10 according to the new 2021 cutoffs and previous 2012-2014 cutoffs are presented below (Table 2).

Table 2: Disease Activity Status Based on JADAS-10 and cJADAS-10 Criteria

	2021 cutoffs		2012-2014 cutoffs	
Disease activity state	JADAS-10	cJADAS-10	JADAS-10	cJADAS-10
Polyarthritis				
Inactive disease	<2.7	<2.5	<1.0	<1.0
Minimal disease activity	2.8-6.0	2.6-5.0	1.1-3.8	1.1-2.5
Moderate disease activity	6.1-17.0	5.1-16.0	3.9-10.5	2.51-8.5
High disease activity	>17.0	>16.0	>10.5	>8.5

- Proportion of patients with inactive disease: Inactive disease is determined by using the modified ACR criteria (Wallace 2011). Specifically, inactive disease is defined as:
  - No joints with active arthritis.
  - No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA.
  - No active uveitis as defined by the SUN Working Group (Jabs 2005).

- Physician's global assessment of disease activity score of best possible on the scale used.
- Duration of morning stiffness of <15 minutes.

The above parameters for effectiveness assessments are routine parameters used in clinical care and/or in clinical studies, which have been shown to be reliable indicators for disease activity and/or improvement of disease activity. (Consolaro 2016; Consolaro 2012; Consolaro 2009; Giannini 1997; McErlane 2013; Trincianti 2021; Wallace 2004)

8.3.3.4. Drug Discontinuation

In the BiKeR registry, the decision of drug discontinuation is made by the treating physician independent of the registry. Dates for starting and ending a biologic medication are recorded on the registry CRFs by the treating physician at each visit when applicable. In case of termination of therapy, a separate form is completed to record the reason for termination (including lack of effectiveness, request of the patient, side effects/intolerance, remission of the disease, and other reasons) and the subsequent treatment modification. Patients continue to be followed by the BiKeR registry after drug discontinuation.

In the case of "remission of the disease" as reason for discontinuation, the patient is followed for disease flare. As this is an observational registry, the diagnosis of disease flare and restart of any treatment are determined by the treating physician. The decision of the treating physician to restart any other treatment because of a flare is recorded on the BiKeR CRF.

For this PASS, data on GLM discontinuation, remission and disease flare/retreatment will be obtained from the BiKeR registry for the GLM cohort.

8.3.3.5. Growth and Development

Height and body weight are routinely measured and recorded on the CRFs at baseline and each follow-up visit in the BiKeR registry.

For this PASS, data on height and weight for the GLM cohort will be extracted every 6 months from the registry database.

8.3.4. Potential Confounders

8.3.4.1. Covariates

Multiple covariates are recorded for each study participant in order to characterize the study population and evaluate these factors as potential confounders.

This section is focused on description of potential confounders for the primary safety outcomes (serious infections, malignancies, and autoimmune processes), for which a sufficient number of events are anticipated to accrue to support multivariate adjustment in the final analyses. For secondary safety endpoints, no multivariate analyses are planned, therefore their potential confounders are not described.

Since each primary safety outcome has its own set of potential confounders, they are described separately for each outcome in the following 3 tables. Table 3 to Table 5 list the potential confounders for each outcome based on previous knowledge and literature, and covariates that are measured in the BiKeR registry, as well as those that are not captured in the registry.

Table 3: Potential Confounders for Serious Infections

Potential confounders*	Covariates measured in BiKeR**
Younger age	Age (date of birth)
Therapy and duration with biologic agents (ETA or ADA)	History of treatments with biologics
Therapy and duration with corticosteroids, DMARD	History of treatments with corticosteroids, DMARD
JIA disease duration,	Duration of JIA since diagnosis
JIA disease severity/activity	JIA disease severity/activity measures
Comorbidities	History of comorbidities

*Becker 2017; Beukelman 2012; Davies 2015; Walters 2015
**: As in all observational studies, the possibility exists that there may be some unknown unmeasured confounders.

Table 4: Potential Confounders for Malignancies

Potential confounders*	Covariates measured in BiKeR**
Age	Age (date of birth)
Previous treatment and duration with biologic agents	History of treatments with biologics
Previous treatment and duration with corticosteroids and DMARD	History of treatments with corticosteroids, DMARD
JIA disease duration	Duration of JIA since diagnosis
JIA disease activity	JIA disease severity/activity measures
Chronic viral infections	History of chronic viral infections
Family history of malignancies	Not captured

*: Diak 2010; Nordstrom 2012; Simard 2010
**: As in all observational studies, the possibility exists that there may also be some unknown unmeasured confounders.

Table 5: Potential Confounders for Autoimmune Processes

Potential confounders*	Confounders measured in BiKeR**
Age	Age (date of birth)
Female gender	Gender
Ethnicity	Race/ethnicity
Previous infection	History of infections
Having other autoimmune disease	History of other autoimmune disease(s)
Medications	History of medications
Smoking	Not captured
Genetic factors/family history of autoimmune diseases	Not captured

*: Cooper 1999; Cooper 1998; Dooley 2003; Tobón 2010
**: As in all observational studies, the possibility exists that there may also be some unknown unmeasured confounders.

For this PASS, information on the following relevant covariates will be extracted from the BiKeR registry database at time of cohort entry (In the event that a patient changes therapy and qualifies for entry into a different exposure cohort, time-varying covariates, such as disease severity, comorbidity, and concomitant medications, are updated at that time).

- Age (date of birth): Age will be defined as age at the time of enrollment into an inception cohort. It will be calculated as date of enrollment minus date of birth.
- Sex.
- Race/Ethnicity.
- Duration of disease since diagnosis: Duration of disease since diagnosis will be calculated as date of enrollment minus date of first diagnosis.
- Disease severity:
  - Physician's global assessment of disease activity (VAS)
  - Parent/patient's global assessment of disease Activity (VAS)
  - Parent/patient assessment of pain (VAS)
  - CHAQ, German version
  - Number of joints with active arthritis defined as swollen and/or tender joints with limited range of motion
  - Erythrocyte sedimentation rate as available
  - CRP as available
  - Duration of morning stiffness
  - JADAS-10: a composite measure of disease severity/activity.
- Comorbidity: The available information on comorbidities including history of infection, uveitis, allergies, and psoriasis.
- History of treatments with biologics: The initiation and ending date of current and previous biologic therapies.
- Co-medications (history of previous relevant medications): The initiation and ending date of current and previous non-biologic therapies for JIA including NSAIDs, corticosteroids, and MTX.

8.4. Data Sources

The data source for determining study exposures, study outcomes, and all relevant covariates is the well-established German BiKeR registry. This PASS will use the data collected in the BiKeR registry to monitor long-term safety of GLM use in patients with pJIA in comparison to other anti-TNFs and MTX therapies. See Section 8.1.1 for description of the registry.

Study Procedures:

For this PASS, there are no specific operational procedures beyond those described for the general BiKeR Registry (Section 8.1.1). All relevant data will be extracted from the BiKeR registry

database periodically. Data will be analyzed, and progress reports will be prepared on an annual basis.

8.5. Study Size

This PASS will include all eligible patients who initiate GLM for the treatment of pJIA in Germany and who are registered in the BiKeR registry in the first 5 years of the study. Based on the registry's previous experience with other biologics and based on marketing forecast data for GLM, it is anticipated that this PASS will enroll about 200 GLM-treated patients with pJIA during the first 5 years of the study. The actual study size will depend on the market uptake of GLM for the treatment of pJIA in Germany. Similarly, for the primary comparison cohort, this PASS seeks to enroll 2 contemporary initiators of other anti-TNFs (ETA or ADA or their biosimilars) for each GLM initiator (approximately 400 other anti-TNF exposed patients). This PASS will also enroll up to 500 contemporary initiators of MTX as the secondary comparison group. In addition, a historic anti-TNF cohort of 2,158 patients with pJIA was already enrolled in the BiKeR registry and will be used in this PASS to provide additional context for the safety outcomes. No formal prior hypothesis will be tested in this PASS. Therefore, no formal calculation of power is applicable.

Rather than test formal hypotheses, the analytic framework for this PASS is risk estimation. For risk estimation studies with a finite sample size, such as this one, it is possible to illustrate the precision of plausible relative risk (RR) estimates for the primary study outcomes over a range of assumptions. Key assumptions for this exercise include the person time at risk for both exposed and comparator cohorts, the expected incidence rate of the study outcome in the comparator cohort, and the range of plausible RR point estimates.

The precisions of potential results are calculated for 2 primary safety endpoints, serious infection and malignancy (as examples), comparing GLM exposure to the primary comparator, contemporary anti-TNF exposure. For serious infection endpoint, the risk window is time on cohort-defining therapy plus 90 days after end of therapy. Assuming each patient with pJIA contributes 3 PYs of observation, 200 GLM patients in the study would accrue 600 PYs, and the 400 other anti-TNF patients would accrue 1,200 PYs. Within the BiKeR registry, the risk of serious infection among patients treated with ETA or ADA was reported to range from approximately 0.5 to 1 per 100 PYs (Klotsche 2016). Based on these assumptions, Table 6 below shows the precision, upper and lower limits of 95% CIs, of potential RRs for serious infection, calculated using Rothman's Episheet program (Rothman 1998).

Table 6: Precision (95% CIs) of Potential RRs for Serious Infection, GLM vs Contemporary Anti-TNF Cohort

	Incidence Rate of Serious Infection in Comparator Group	
Potential RR Point Estimate	0.5/100 PYs	1/100 PYs
1.0	0.25, 4.0	0.38, 2.66
2.0	0.65, 6.2	0.90, 4.45
3.0	1.07, 8.43	1.44, 6.23
4.0	1.50, 10.66	2.00, 8.00

The precision of potential RRs was calculated for the endpoint of all-cause malignancy as well. For this outcome, the analytic approach in prior BiKeR studies has been to consider all follow-up time as person time at risk, regardless of current exposure status. In this context, the 200 GLM patients would contribute 1,000 PYs of observation (patients are followed for 5 years) and the 400 other anti-TNF comparator patients would contribute 2,000 PYs. Prior research from BiKeR registry has indicated the risk of malignancy for ADA and ETA exposures ranges from approximately 1/1,000 PYs to 1/500 PYs (Klotsche 2016). Based on these assumptions, Table 7 below shows the precision, 95% CIs of potential RRs for all-cause malignancy, calculated using Rothman's Episheet program (Rothman 1998).

Table 7: Precision (95% CIs) of Potential RRs for All-cause Malignancy, GLM vs Contemporary Anti-TNF Cohort

	Incidence rate of all cause malignancy in comparator group	
Potential RR Point Estimate	1/1000 PYs	1/500 PYs
1.0	0.09, 11.03	0.18, 5.46
2.0	0.28, 14.2	0.5, 8.0
3.0	0.50, 17.95	0.85, 10.63
4.0	0.73, 21.84	1.20, 13.28

8.6. Data Collection and Management

For this PASS, data management will be handled by the BiKeR staff. The company does not own and has no access to the registry data. Only aggregate tables and study reports will be sent to the company periodically by the registry.

8.7. Data Analysis

Statistical analyses will be performed by or under the authority of the sponsor. A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections.

This section outlines the analytic plans to address the PASS objectives. The final approach will be described in a stand-alone SAP, which will be completed before any comparative analyses are undertaken.

All patients who are enrolled into 1 of the 4 cohorts and who have completed standardized data documentation prior to starting cohort defining medications will be included in the baseline descriptive analysis. Patients who have at least 1 follow-up assessment after receiving the cohort defining medication will be included in the safety analysis (all cohorts) and effectiveness analysis (GLM cohort).

8.7.1. Descriptive Analysis

Basic descriptive tabulations and statistical analyses will be performed in each report:

- For each contemporary cohort, annual enrollment along with cumulative person-years accrued will be described.
- Demographic and baseline characteristics of all patients will be described by cohort using mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for discrete variables, respectively.
- For each primary safety endpoint, number of event and incidence rate will be calculated for each cohort. Subgroup analysis stratified by history of prior anti-TNF use, disease severity, and disease duration will be conducted if data permit.
- For each secondary safety endpoint, number of events and incidence rate will be calculated for the GLM cohort, contemporary anti-TNF cohort and contemporary MTX cohort. Because a subset of the secondary safety outcomes are newly added to the registry's CRF for the prospective portion of this PASS, for the historic anti-TNF cohort these newly added events are not systematically collected in the past. Thus, frequencies and incidence rates in the historic anti-TNF cohort will be calculated only for those secondary safety endpoints that were systematically ascertained during the historic observation period.
- For the GLM cohort, magnitude of treatment response (as determined by PedACR 30, 50, 70, and 90, JADAS-10, and proportion of patients with inactive disease) will be described by comparing disease activity measurements at Months 3, 6, 12, and 24 to baseline measurements. If data permit, stratified analyses will be done by on/off label use of GLM.
- For the GLM cohort, treatment duration, proportion of GLM discontinuation, and reasons for discontinuation will be described. For patients who discontinue GLM after remission, time to disease flare and retreatment will be described.
- For the GLM cohort, height and body weight will be analyzed against average height and weight in respective age and gender categories in Germany. Body mass index (weight in kg/height squared in meter) will be calculated. Age and sex specific z scores will be used for the weight, height, and BMI analyses. A patient's height z-score is obtained by comparing the patient's height (cm) with the average height from the German pediatric population with the same age and sex.

The equation to calculate the z-score for height is

$$Z = \frac{\text{observed height - age and sex adjusted avg. height}}{\text{standard deviation}}$$

Similarly, a patient's weight z-score is obtained by comparing the patient's weight (kg) with the average weight from the German pediatric population with the same age and sex. A patient's BMI z-score is obtained by comparing the patient's BMI with the average BMI from the German pediatric population with the same age and sex.

Because the average height and weight are fairly stable in Germany and no major changes are expected over years, national average values for height and weight for every age are not updated every year. The latest data were published in 2013 by the German Robert Koch Institute (a national

health organization) (Koch-Institut 2013). These data will be used for reference for this PASS. If new data became available in the future, the updated data may be used for the analysis.

8.7.2. Comparative Analyses

Comparative analyses will be conducted for primary safety outcomes in the final report.

8.7.2.1. GLM Cohort Compared to Contemporary Anti-TNF Cohort (Primary Comparison)

The risks of primary safety outcomes will be compared between GLM cohort and contemporary anti-TNF cohort stratified by age, sex, body weight, and history of prior anti-TNF therapy if data permit. Cox proportional hazards regression model will be used to estimate the hazard ratios of primary safety outcomes. Analyses will use time since cohort entry as the primary time axis, using risk windows described in Section 8.2.3.1 for different study outcomes (once exposed always at-risk window for malignancies and 90-day risk window for other safety outcomes).

Potential confounders to be evaluated are described in Section 8.3.4. Evaluation for potential confounders and adjustment for confounding will occur through multivariate model analyses. A change of 10% or more between the crude and the adjusted point estimate will be considered evidence of confounding. Priority for inclusion in the final model will be based on the magnitude of change in estimate between crude and adjusted models that evaluate each individual potential confounder. There are multiple measures for disease severity/activities, and it is likely that they are highly correlated with each other. Therefore, only JADAS-10, the composite disease activity measure, will be included in the multivariate analysis. Other individual disease activity measures will be included in descriptive analyses.

Unmeasured confounders: To assess potential impact of unmeasured confounders, we propose to do sensitivity analyses based on an array of informed assumptions in the final analysis. For example, these analyses would explore the circumstances under which there would be substantial change in the point estimate by varying values for prevalence of the unmeasured confounder across treatment groups and strength of association between confounder and outcome. (Schneeweiss 2006).

Time-varying analysis: Relevant time-varying covariates will be accounted for using Cox proportional hazards regression models. An advantage of the Cox model is its ability to include covariates that change over time. At each event, the model will compare covariate values for the subject that experienced the event to the covariate values of all other patients at risk to experience the event (Therneau 2017). Note however that for covariates that could reflect drug effects (eg, disease activity), these will be updated only at the time of cohort entry (or switch to a new treatment cohort). Disease activity (or other potential consequences of drug effect, such as co-medication use) may well be an intermediate variable in the causal pathway between drug exposure and outcome. Control for an intermediate variable is not recommended; it can result in overadjustment and generally biases the results towards the null. Therefore, this type of adjustment could increase rather than decrease study bias (Rothman 1998; Schisterman 2009; Vanderweele 2009).

Consequently, covariates that could reflect treatment effect will be updated only periodically, at time of switch to a new study drug.

Correlation. Given the nature of clinical care, it is expected that some subjects will switch cohorts during follow up, and that observations on the same subjects before and after the switch may correlate in some way. When this correlation is not accounted for, the standard errors of the survival estimates underestimate the true variability, or in other words, the observed confidence intervals around hazard ratios will be artificially narrow. A common method to account for observations nested within the same subject for a Cox proportional hazards model is known as the marginal models approach. In this approach the standard variance estimate is replaced with one which is corrected for the possible correlations (a robust sandwich covariance matrix estimate). This method allows for flexibility in the formation of strata, manipulation of the time scale, and has a well-developed estimator of variance (Therneau 2000). This approach will be considered in the final analysis and further described in the SAP.

Missing data. To deal with missing data, the patterns and potential determinants of missing data will first be evaluated. Depending on the extent of missing data, the primary analysis will use complete data. Alternative approaches to handle missing data in the final analyses, such as multiple imputation (Pedersen 2017), will depend on data characteristics including the determinants and extent of missing data, size of the data set, and number of outcomes. The approach to be used will be further described in the SAP. For the purpose of these analyses, we assume that information on exposures and outcomes is complete, and these analyses are used to handle missing data in covariates.

8.7.2.2. GLM Cohort Compared to Contemporary MTX Cohort (Secondary Comparison)

There are concerns that patients initiating GLM are different from patients initiating MTX in terms of disease severity, disease duration, treatment history, comorbidity, and other characteristics. In addition, most GLM patients are likely to have received MTX previously or concomitantly, which makes the 2 cohorts incomparable. However, it is of value to have a biologic naïve cohort as a comparison to identify any potential risks associated with anti-TNF agents. If inspection of baseline characteristics suggests that the 2 groups are reasonably similar, stratified analyses, and multivariate analyses may be performed as described above for the GLM vs contemporary anti-TNF cohorts (more analysis details will be provided in the SAP). However, this comparison should be interpreted cautiously and will only be considered as a secondary comparison.

Statistical analyses will be performed with the contractor PPD [redacted] This includes analyses for regular study reports as well as publications.

8.7.3. Statistical Methods

For the analyses presented in the progress reports, patients from the other anti-TNF and MTX comparator cohorts are frequency matched by body weight and only descriptive analyses are performed (see Section 8.7.1).

For the purpose of the final report, an alternative matching technique may be considered. If data permit, modelled statistical analyses to adjust for potential confounders will be conducted and a detailed SAP will be prepared.

8.8. Quality Control

8.8.1. Quality Assurance and Quality Control of the Database

Standard operating procedures or internal process guidance at each research center and/or coordinating center should be adhered to for the conduct of the study. These procedures should include internal quality audits, 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 any other relevant process documents related to data transfer and data pooling, if applicable.

For this PASS, quality control is handled by the BiKeR registry. Aggregate tables and study progress reports are generated by the registry and submitted to the company on a regular basis.

By signing this PASS protocol, the BiKeR registry is responsible for implementing and maintaining a quality management system with written procedures and standard operating procedures (SOPs) to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical and Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

8.9. Strengths and Limitations of the Research Methods

Strength: Information is captured by certified pediatric rheumatologists. Misclassification of the outcomes should therefore be low. In addition, it has been shown that he BiKeR patient population is generally comparable to other MTX- and biologic-eligible JIA populations in European Union countries in terms of age of onset, age of treatment initiation, gender, history of uveitis, HLA B27 positivity, pretreatment and co-treatment with steroids and MTX.

JIA subcategory distribution is affected by treatment decision and approval of drug. Since GLM is approved for polyarticular JIA, only those JIA categories are included.

Thus, the BiKeR population seems representative of the European Union JIA population and results are likely to be generalizable to the European Union JIA population (Kearsley-Fleet 2016; Southwood 2011; Tarkiainen 2015).

Limitations: This is a non-interventional observational study without randomization. There are certain limitations or biases that could be introduced in an observational study design such as indication bias or channeling bias due to lack of randomization. There are a few additional limitations specific for this PASS, and they are described as follows:

- The accrual of patients for this PASS is constrained by the low prevalence of pJIA and real-life future use of GLM for this indication. Several of the study outcomes occur rarely (eg,

malignancy). As a consequence, it is expected that the number of outcomes for some endpoints will be sparse, which will limit the precision of study results.

- Effectiveness is measured in an unblinded fashion, as is the standard in usual clinical care. The effectiveness measures are subject to reporting biases from both patients and physicians.
- Because this is an observational study, the actual frequency of clinical follow up will depend on practice patterns in the usual care setting. This could lead to incomplete data collection, which is out of control of the company. Also, because this PASS is a secondary data collection study, it is limited to the data collected in the routine practice of the BiKeR registry.
- GLM may be used as a second-line biologic therapy for pJIA, while ETA or ADA is commonly used as a first-line therapy; therefore, disease severity and characteristics of the patient populations may differ and may not be completely comparable. To mitigate confounding, a subgroup analysis stratified by line therapy will be conducted if data permit.
- Because patients with pJIA typically are started on anti-TNF agents only after MTX is ineffective, comparison of GLM with MTX may be biased due to confounding by indication. Accordingly, the contemporary MTX cohort will be used as a secondary comparison group.
- A few secondary safety outcomes were not specifically listed in the version of the registry CRF used prior to the start of this PASS. The registry has added these AE terms to the CRF for systematic data collection for the prospective portion of this PASS. To minimize the potential for information bias, incidence rates for these events will be calculated only for the GLM cohort, contemporary anti-TNF cohort and contemporary MTX cohort. For the historic anti-TNF cohort, these events were not systematically collected in the past and thus incidence rates for these events will not be calculated.
- Other limitations include potential under-ascertainment of pregnancy loss and imperfect confounding adjustment due to data limitations such as imperfect data on measured confounders and missing data on unmeasured confounders. Also, because the number of variables that a multivariate model can support depends on the number of outcomes observed, for any outcome with sparse events, the number of potential confounders that can be included in the multivariate model may be limited.

9. PROTECTION OF HUMAN SUBJECTS

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

9.1. Informed Consent

Informed consent is signed in the context of participating in the BiKeR registry (see Section 8.1.1). Because this PASS is a secondary data collection study that uses the data collected by the BiKeR registry, no additional informed consent is needed for this study.

10. COLLECTION AND REPORTING OF SAFETY DATA

This study is a non-interventional study based on the BiKeR registry and uses data that already exist in this registry database. It is designed to assess the relation between golimumab exposure and the adverse events of interest based on aggregate analysis.

Data from the registry will be provided to Janssen in the form of aggregate safety data tables only. Based on the format of the data provided, it is not possible to link a particular product and medical event for any identifiable individual. Thus, it will not be possible to identify any adverse drug reactions.

Any AE received through tabulated data will be included in the clinical study report.

The study results will be assessed for medically important results.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a clinical study report generated by the sponsor. Patient identifiers will not be used in the publication of results. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Results of this PASS will be submitted to a peer-reviewed journal for publication and submitted for presentations on national and international conferences. Core publication will be authored by the investigators who contribute significantly to the implementation and conduct of the BiKeR registry and personnel who contribute substantially to the design, interpretation or analysis of this PASS. Academic standards, including the ICMJE authorship criteria, will be followed. The principal investigator has the right to independently prepare that publication. The company is entitled to review the results and interpretations included in the manuscript and provide comment prior to submission of the manuscript for publication.

Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the participating physician) shall be the property of the sponsor as author and owner of copyright in such work.

For this PASS, progress reports will be submitted to appropriate EU and local authorities annually during the study, according to the schedule under Milestones (Section 5). Each progress report will include information about the number of patients who have entered in each of the study cohorts, cumulative follow-up time accrued in each cohort, descriptive analyses of baseline demographic and clinical characteristics, counts and incidence rates of each safety outcome of interest tabulated by exposure at cohort entry. For the GLM cohort, disease activity parameters, height, and weight will be described. Information on discontinuation of GLM and reasons for discontinuation, follow-up data of patients after remission will be provided. The final study report, which may include comparative analyses if data permit, will be submitted within 6 months of the end of data collection.

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13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1. Annex 1.1: List of Standalone Documents

Title	Reference No	Date
List of participating centers	EDMS-RIM-1518603	20 Jan 2025

14. ADDITIONAL INFORMATION

14.1. MedDRA TERMS FOR SAFETY OUTCOMES FOR BiKeR PASS (V2.0)

Outcomes for BiKeR PASS v2.0	**MedDRA Terms (Version 23.0)**
Primary safety outcomes	
Serious infections (including opportunistic infections, tuberculosis, and hepatitis B virus reactivation)	System organ classs Infections and infestations (as indicated by the investigator AND Serious flag = Yes) For Opportunistic Infection PTs and Tuberculosis PTs, see list of terms below. Hepatitis B virus reactivation PTs: Hepatitis B Hepatitis B core antigen positive Hepatitis B DNA assay positive Hepatitis B DNA increased Hepatitis B E antigen positive Hepatitis B reactivation Hepatitis B surface antigen positive Hepatitis B virus test positive
Malignancy	Standardised MedDRA query (SMQ) Malignant or unspecified tumours (Narrow)
Autoimmune processes	For Autoimmune Disorders PTs , see list of terms below. Including thyroiditis, autoimmune diabetes, uveitis, psoriasis, inflammatory bowel disease (IBD), celiac disease, demyelination, as well as systemic lupus erythematosus (SLE)
Exposure during pregnancy	HLT Exposures associated with pregnancy, delivery and lactation
Outcomes for BiKeR PASS v2.0	**MedDRA Terms (Version 23.0)**
Secondary safety outcomes	
Demyelinating disorders	SMQ Demyelination (narrow)
Serious depression including suicidality	SMQs: Depression (excluding suicide and self-injury) (Narrow) Suicide/Self Injury SMQ (Narrow) AND Serious flag = Yes

Serious flag=fulfils the criteria of an SAE (based on International Council for Harmonisation and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use), ie, any untoward medical occurrence that at any dose: results in death, is life-threatening (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is a suspected transmission of any infectious agent via a medicinal product; is medically important

Opportunistic Infection PTs

HLGT_NAME	HLT_NAME	PT_NAME
BACTERIAL INFECTIOUS DISORDERS	ACTINOMYCOTIC INFECTIOUS DISORDERS	ACTINOMYCOSIS
BACTERIAL INFECTIOUS DISORDERS	ACTINOMYCOTIC INFECTIOUS DISORDERS	ACTINOMYCOTIC ABDOMINAL INFECTION
BACTERIAL INFECTIOUS DISORDERS	ACTINOMYCOTIC INFECTIOUS DISORDERS	ACTINOMYCOTIC PULMONARY INFECTION
BACTERIAL INFECTIOUS DISORDERS	ACTINOMYCOTIC INFECTIOUS DISORDERS	ACTINOMYCOTIC SKIN INFECTION
BACTERIAL INFECTIOUS DISORDERS	LEGIONELLA INFECTIONS	LEGIONELLA INFECTION
BACTERIAL INFECTIOUS DISORDERS	LEGIONELLA INFECTIONS	PNEUMONIA LEGIONELLA
BACTERIAL INFECTIOUS DISORDERS	LEGIONELLA INFECTIONS	PONTIAC FEVER
BACTERIAL INFECTIOUS DISORDERS	LISTERIA INFECTIONS	LISTERIA ENCEPHALITIS
BACTERIAL INFECTIOUS DISORDERS	LISTERIA INFECTIONS	LISTERIA SEPSIS
BACTERIAL INFECTIOUS DISORDERS	LISTERIA INFECTIONS	LISTERIOSIS
BACTERIAL INFECTIOUS DISORDERS	LISTERIA INFECTIONS	MENINGITIS LISTERIA
BACTERIAL INFECTIOUS DISORDERS	LISTERIA INFECTIONS	LISTERAEMIA
BACTERIAL INFECTIOUS DISORDERS	NOCARDIA INFECTIONS	NOCARDIA SEPSIS
BACTERIAL INFECTIOUS DISORDERS	NOCARDIA INFECTIONS	NOCARDIOSIS
BACTERIAL INFECTIOUS DISORDERS	NOCARDIA INFECTIONS	PULMONARY NOCARDIOSIS
BACTERIAL INFECTIOUS DISORDERS	BACILLARY INFECTIONS	SHEWANELLA ALGAE BACTERAEMIA

HLGT_NAME	HLT_NAME	PT_NAME
BACTERIAL INFECTIOUS DISORDERS	BACTERIAL INFECTIONS NEC	BREVIBACTERIUM INFECTION
BACTERIAL INFECTIOUS DISORDERS	BACTERIAL INFECTIONS NEC	SPHINGOMONAS PAUCIMOBILIS INFECTION
BACTERIAL INFECTIOUS DISORDERS	BACTERIAL INFECTIONS NEC	SPHINGOMONAS PAUCIMOBILIS BACTERAEMIA
BACTERIAL INFECTIOUS DISORDERS	BACTERIAL INFECTIONS NEC	DELFTIA ACIDOVORANS INFECTION
BACTERIAL INFECTIOUS DISORDERS	BACTERIAL INFECTIONS NEC	ACHROMOBACTER INFECTION
BACTERIAL INFECTIOUS DISORDERS	SERRATIA INFECTIONS	PNEUMONIA SERRATIA
BACTERIAL INFECTIOUS DISORDERS	ACTINOMYCOTIC INFECTIOUS DISORDERS	ACTINOMYCOTIC SEPSIS
BACTERIAL INFECTIOUS DISORDERS	BARTONELLA INFECTIONS	SYSTEMIC BARTONELLOSIS
BACTERIAL INFECTIOUS DISORDERS	VIBRIO INFECTIONS	VIBRIO VULNIFICUS INFECTION
BACTERIAL INFECTIOUS DISORDERS	CAPNOCYTOPHAGA INFECTIONS	CAPNOCYTOPHAGA SEPSIS
BACTERIAL INFECTIOUS DISORDERS	BURKHOLDERIA INFECTIONS	BURKHOLDERIA CEPACIA COMPLEX INFECTION
BACTERIAL INFECTIOUS DISORDERS	SALMONELLA INFECTIONS	AORTITIS SALMONELLA
BACTERIAL INFECTIOUS DISORDERS	SALMONELLA INFECTIONS	ARTHRITIS SALMONELLA
BACTERIAL INFECTIOUS DISORDERS	SALMONELLA INFECTIONS	GASTROENTERITIS SALMONELLA
BACTERIAL INFECTIOUS DISORDERS	SALMONELLA INFECTIONS	MENINGITIS SALMONELLA
BACTERIAL INFECTIOUS DISORDERS	SALMONELLA INFECTIONS	OSTEOMYELITIS SALMONELLA

HLGT_NAME	HLT_NAME	PT_NAME
BACTERIAL INFECTIOUS DISORDERS	SALMONELLA INFECTIONS	PARATYPHOID FEVER
BACTERIAL INFECTIOUS DISORDERS	SALMONELLA INFECTIONS	PNEUMONIA SALMONELLA
BACTERIAL INFECTIOUS DISORDERS	SALMONELLA INFECTIONS	SALMONELLA BACTERAEMIA
BACTERIAL INFECTIOUS DISORDERS	SALMONELLA INFECTIONS	SALMONELLA SEPSIS
BACTERIAL INFECTIOUS DISORDERS	SALMONELLA INFECTIONS	SALMONELLOSIS
BACTERIAL INFECTIOUS DISORDERS	SALMONELLA INFECTIONS	TYPHOID FEVER
FUNGAL INFECTIOUS DISORDERS	ALLESCHERIA INFECTIONS	ALLESCHERIOSIS
FUNGAL INFECTIOUS DISORDERS	ASPERGILLUS INFECTIONS	ASPERGILLOMA
FUNGAL INFECTIOUS DISORDERS	ASPERGILLUS INFECTIONS	ASPERGILLOSIS ORAL
FUNGAL INFECTIOUS DISORDERS	ASPERGILLUS INFECTIONS	ASPERGILLUS INFECTION
FUNGAL INFECTIOUS DISORDERS	ASPERGILLUS INFECTIONS	BRONCHOPULMONARY ASPERGILLOSIS
FUNGAL INFECTIOUS DISORDERS	ASPERGILLUS INFECTIONS	CEREBRAL ASPERGILLOSIS
FUNGAL INFECTIOUS DISORDERS	ASPERGILLUS INFECTIONS	MENINGITIS ASPERGILLUS
FUNGAL INFECTIOUS DISORDERS	ASPERGILLUS INFECTIONS	ORO-PHARYNGEAL ASPERGILLOSIS
FUNGAL INFECTIOUS DISORDERS	ASPERGILLUS INFECTIONS	SINUSITIS ASPERGILLUS
FUNGAL INFECTIOUS DISORDERS	BLASTOMYCES INFECTIONS	BLASTOMYCOSIS

HLGT_NAME	HLT_NAME	PT_NAME
FUNGAL INFECTIOUS DISORDERS	BLASTOMYCES INFECTIONS	EPIDIDYMITIS BLASTOMYCES
FUNGAL INFECTIOUS DISORDERS	BLASTOMYCES INFECTIONS	OSTEOMYELITIS BLASTOMYCES
FUNGAL INFECTIOUS DISORDERS	BLASTOMYCES INFECTIONS	PNEUMONIA BLASTOMYCES
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	BLADDER CANDIDIASIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	URINARY TRACT CANDIDIASIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	CANDIDA ENDOPHTHALMITIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	CANDIDA OSTEOMYELITIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	CANDIDA PNEUMONIA
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	CANDIDA RETINITIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	CANDIDA SEPSIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	ENDOCARDITIS CANDIDA
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	GASTROINTESTINAL CANDIDIASIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	HEPATIC CANDIDIASIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	HEPATOSPLENIC CANDIDIASIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	MENINGITIS CANDIDA
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	OESOPHAGEAL CANDIDIASIS

HLGT_NAME	HLT_NAME	PT_NAME
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	PERITONEAL CANDIDIASIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	PROCTITIS MONILIAL
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	RESPIRATORY MONILIASIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	SPLENIC CANDIDIASIS
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	SYSTEMIC CANDIDA
FUNGAL INFECTIOUS DISORDERS	CANDIDA INFECTIONS	CEREBRAL CANDIDIASIS
FUNGAL INFECTIOUS DISORDERS	COCCIDIOIDES INFECTIONS	COCCIDIOIDES ENCEPHALITIS
FUNGAL INFECTIOUS DISORDERS	COCCIDIOIDES INFECTIONS	COCCIDIOIDOMYCOSIS
FUNGAL INFECTIOUS DISORDERS	COCCIDIOIDES INFECTIONS	CUTANEOUS COCCIDIOIDOMYCOSIS
FUNGAL INFECTIOUS DISORDERS	COCCIDIOIDES INFECTIONS	MENINGITIS COCCIDIOIDES
FUNGAL INFECTIOUS DISORDERS	CRYPTOCOCCAL INFECTIONS	CRYPTOCOCCAL CUTANEOUS INFECTION
FUNGAL INFECTIOUS DISORDERS	CRYPTOCOCCAL INFECTIONS	CRYPTOCOCCAL FUNGAEMIA
FUNGAL INFECTIOUS DISORDERS	CRYPTOCOCCAL INFECTIONS	CRYPTOCOCCOSIS
FUNGAL INFECTIOUS DISORDERS	CRYPTOCOCCAL INFECTIONS	DISSEMINATED CRYPTOCOCCOSIS
FUNGAL INFECTIOUS DISORDERS	CRYPTOCOCCAL INFECTIONS	GASTROENTERITIS CRYPTOCOCCAL
FUNGAL INFECTIOUS DISORDERS	CRYPTOCOCCAL INFECTIONS	MENINGITIS CRYPTOCOCCAL

HLGT_NAME	HLT_NAME	PT_NAME
FUNGAL INFECTIOUS DISORDERS	CRYPTOCOCCAL INFECTIONS	NEUROCRYPTOCOCCOSIS
FUNGAL INFECTIOUS DISORDERS	CRYPTOCOCCAL INFECTIONS	PNEUMONIA CRYPTOCOCCAL
FUNGAL INFECTIOUS DISORDERS	CRYPTOCOCCAL INFECTIONS	OSSEOUS CRYPTOCOCCOSIS
FUNGAL INFECTIOUS DISORDERS	EXSEROHILUM INFECTIONS	EXSEROHILUM INFECTION
FUNGAL INFECTIOUS DISORDERS	EXSEROHILUM INFECTIONS	MENINGITIS EXSEROHILUM
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	MUCORMYCOSIS
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	CUTANEOUS MUCORMYCOSIS
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	GASTROINTESTINAL MUCORMYCOSIS
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	PULMONARY MUCORMYCOSIS
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	RHINOCEREBRAL MUCORMYCOSIS
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	ZYGOMYCOSIS
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	GEOTRICHUM INFECTION
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	FUSARIUM INFECTION
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	MYCETOMA MYCOTIC
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	MYCOTIC ANEURYSM
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	MYOCARDITIS MYCOTIC

HLGT_NAME	HLT_NAME	PT_NAME
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	MYCOTIC ENDOPHTHALMITIS
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	MYCOTIC CORNEAL ULCER
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	PULMONARY TRICHOSPORONOSIS
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	SCOPULARIOPSIS INFECTION
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	NEOSCYTALIDIUM INFECTION
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	PENICILLIUM INFECTION
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	PHAEOHYPHOMYCOSIS
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	PHAEOHYPHOMYCOTIC BRAIN ABSCESS
FUNGAL INFECTIOUS DISORDERS	FUNGAL INFECTIONS NEC	AUREOBASIDIUM PULLULANS INFECTION
FUNGAL INFECTIOUS DISORDERS	HISTOPLASMA INFECTIONS	ACUTE PULMONARY HISTOPLASMOSIS
FUNGAL INFECTIOUS DISORDERS	HISTOPLASMA INFECTIONS	CHRONIC PULMONARY HISTOPLASMOSIS
FUNGAL INFECTIOUS DISORDERS	HISTOPLASMA INFECTIONS	ENDOCARDITIS HISTOPLASMA
FUNGAL INFECTIOUS DISORDERS	HISTOPLASMA INFECTIONS	HISTOPLASMOSIS
FUNGAL INFECTIOUS DISORDERS	HISTOPLASMA INFECTIONS	HISTOPLASMOSIS CUTANEOUS
FUNGAL INFECTIOUS DISORDERS	HISTOPLASMA INFECTIONS	HISTOPLASMOSIS DISSEMINATED
FUNGAL INFECTIOUS DISORDERS	HISTOPLASMA INFECTIONS	MENINGITIS HISTOPLASMA

HLGT_NAME	HLT_NAME	PT_NAME
FUNGAL INFECTIOUS DISORDERS	HISTOPLASMA INFECTIONS	PERICARDITIS HISTOPLASMA
FUNGAL INFECTIOUS DISORDERS	HISTOPLASMA INFECTIONS	PRESUMED OCULAR HISTOPLASMOSIS SYNDROME
FUNGAL INFECTIOUS DISORDERS	HISTOPLASMA INFECTIONS	RETINITIS HISTOPLASMA
FUNGAL INFECTIOUS DISORDERS	PARACOCCIDIOIDES INFECTIONS	PARACOCCIDIOIDES INFECTION
FUNGAL INFECTIOUS DISORDERS	PARACOCCIDIOIDES INFECTIONS	PULMONARY PARACOCCIDIOIDOMYCOSIS
FUNGAL INFECTIOUS DISORDERS	PNEUMOCYSTIS INFECTIONS	PNEUMOCYSTIS JIROVECII INFECTION
FUNGAL INFECTIOUS DISORDERS	PNEUMOCYSTIS INFECTIONS	PNEUMOCYSTIS JIROVECII PNEUMONIA
FUNGAL INFECTIOUS DISORDERS	PSEUDALLESCHERIA INFECTIONS	PSEUDALLESCHERIA INFECTION
FUNGAL INFECTIOUS DISORDERS	PSEUDALLESCHERIA INFECTIONS	PSEUDALLESCHERIA SEPSIS
FUNGAL INFECTIOUS DISORDERS	SPOROTHRIX INFECTIONS	CUTANEOUS SPOROTRICHOSIS
FUNGAL INFECTIOUS DISORDERS	SPOROTHRIX INFECTIONS	SPOROTRICHOSIS
HELMINTHIC DISORDERS	NEMATODE INFECTIONS	DIROFILARIASIS
INFECTIONS-PATHOGEN UNSPECIFIED	LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	HAEMORRHAGIC PNEUMONIA
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	ATYPICAL MYCOBACTERIAL INFECTION
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	ATYPICAL MYCOBACTERIAL LYMPHADENITIS

HLGT_NAME	HLT_NAME	PT_NAME
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	ATYPICAL MYCOBACTERIAL PNEUMONIA
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	ATYPICAL MYCOBACTERIUM PERICARDITIS
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	MYCOBACTERIAL INFECTION
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	MYCOBACTERIAL PERITONITIS
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	MYCOBACTERIUM ABSCESSUS INFECTION
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	MYCOBACTERIUM AVIUM COMPLEX IMMUNE RESTORATION DISEASE
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	MYCOBACTERIUM AVIUM COMPLEX INFECTION
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	MYCOBACTERIUM CHELONAE INFECTION
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	MYCOBACTERIUM FORTUITUM INFECTION
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	MYCOBACTERIUM KANSASII INFECTION
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	MYCOBACTERIUM MARINUM INFECTION
MYCOBACTERIAL INFECTIOUS DISORDERS	ATYPICAL MYCOBACTERIAL INFECTIONS	MYCOBACTERIUM ULCERANS INFECTION
MYCOBACTERIAL INFECTIOUS	TUBERCULOUS INFECTIONS	DISSEMINATED BACILLUS CALMETTE-GUERIN INFECTION

HLGT_NAME	HLT_NAME	PT_NAME
DISORDERS		
MYCOPLASMAL INFECTIOUS DISORDERS	UREAPLASMA INFECTIONS	UREAPLASMAL VULVOVAGINITIS
MYCOPLASMAL INFECTIOUS DISORDERS	UREAPLASMA INFECTIONS	UREAPLASMA CERVICITIS
MYCOPLASMAL INFECTIOUS DISORDERS	UREAPLASMA INFECTIONS	UREAPLASMA INFECTION
PROTOZOAL INFECTIOUS DISORDERS	PROTOZOAL INFECTIONS NEC	PROTOTHECOSIS
PROTOZOAL INFECTIOUS DISORDERS	CRYPTOSPORIDIA INFECTIONS	BILIARY TRACT INFECTION CRYPTOSPORIDIAL
PROTOZOAL INFECTIOUS DISORDERS	CRYPTOSPORIDIA INFECTIONS	CRYPTOSPORIDIOSIS INFECTION
PROTOZOAL INFECTIOUS DISORDERS	CRYPTOSPORIDIA INFECTIONS	GASTROENTERITIS CRYPTOSPORIDIAL
PROTOZOAL INFECTIOUS DISORDERS	TOXOPLASMA INFECTIONS	CEREBRAL TOXOPLASMOSIS
PROTOZOAL INFECTIOUS DISORDERS	TOXOPLASMA INFECTIONS	EYE INFECTION TOXOPLASMAL
PROTOZOAL INFECTIOUS DISORDERS	TOXOPLASMA INFECTIONS	HEPATITIS TOXOPLASMAL
PROTOZOAL INFECTIOUS DISORDERS	TOXOPLASMA INFECTIONS	MENINGITIS TOXOPLASMAL
PROTOZOAL INFECTIOUS DISORDERS	TOXOPLASMA INFECTIONS	MYOCARDITIS TOXOPLASMAL
PROTOZOAL INFECTIOUS DISORDERS	TOXOPLASMA INFECTIONS	PNEUMONIA TOXOPLASMAL
PROTOZOAL INFECTIOUS DISORDERS	TOXOPLASMA INFECTIONS	TOXOPLASMOSIS
PROTOZOAL INFECTIOUS DISORDERS	TOXOPLASMA INFECTIONS	DISSEMINATED TOXOPLASMOSIS

HLGT_NAME	HLT_NAME	PT_NAME
VIRAL INFECTIOUS DISORDERS	ADENOVIRAL INFECTIONS	ADENOVIRUS REACTIVATION
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS CHORIORETINITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS COLITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS DUODENITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS ENTERITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS ENTEROCOLITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS GASTRITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS GASTROENTERITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS GASTROINTESTINAL INFECTION
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS HEPATITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS INFECTION
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS MYELOMENINGORADI CULITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS MYOCARDITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS OESOPHAGITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS PANCREATITIS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS PERICARDITIS

HLGT_NAME	HLT_NAME	PT_NAME
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS VIRAEMIA
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	DISSEMINATED CYTOMEGALOVIRAL INFECTION
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	ENCEPHALITIS CYTOMEGALOVIRUS
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	PNEUMONIA CYTOMEGALOVIRAL
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS GASTROINTESTINAL ULCER
VIRAL INFECTIOUS DISORDERS	CYTOMEGALO VIRAL INFECTIONS	CYTOMEGALOVIRUS NEPHRITIS
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	CHRONIC ACTIVE EPSTEIN- BARR VIRUS INFECTION
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	EPSTEIN BARR VIRUS POSITIVE MUCOCUTANEOUS ULCER
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	EPSTEIN-BARR VIRAEMIA
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	EPSTEIN-BARR VIRUS ASSOCIATED LYMPHOMA
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	EPSTEIN-BARR VIRUS ASSOCIATED LYMPHOPROLIFERATIV E DISORDER
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	EPSTEIN-BARR VIRUS INFECTION
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	EPSTEIN-BARR VIRUS INFECTION REACTIVATION
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	HEPATITIS INFECTIOUS MONONUCLEOSIS
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	INFECTIOUS MONONUCLEOSIS

HLGT_NAME	HLT_NAME	PT_NAME
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	ORAL HAIRY LEUKOPLAKIA
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	POST TRANSPLANT LYMPHOPROLIFERATIV E DISORDER
VIRAL INFECTIOUS DISORDERS	EPSTEIN-BARR VIRAL INFECTIONS	X-LINKED LYMPHOPROLIFERATIV E SYNDROME
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	COLITIS HERPES
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	DISSEMINATED VARICELLA ZOSTER VACCINE VIRUS INFECTION
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	GASTRITIS HERPES
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES OESOPHAGITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES OPHTHALMIC
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SEPSIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SIMPLEX COLITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SIMPLEX ENCEPHALITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SIMPLEX GASTRITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPEX SIMPLEX HEPATITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SIMPLEX MENINGITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SIMPLEX MENINGOENCEPHALITI S
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SIMPLEX MENINGOMYELITIS

HLGT_NAME	HLT_NAME	PT_NAME
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SIMPLEX NECROTISING RETINOPAHTY
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SIMPLEX OESOPHAGITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SIMPLEX PNEUMONIA
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SIMPLEX SEPSIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES SIMPLEX VISCERAL
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES ZOSTER CUTANEOUS DISSEMINATED
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES ZOSTER DISSEMINATED
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES ZOSTER INFECTION NEUROLOGICAL
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES ZOSTER MENINGITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES ZOSTER MENINGOENCEPHALITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES ZOSTER MENINGOMYELITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES ZOSTER OPHTHALMIC
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES ZOSTER NECROTISING RETINOPATHY
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	PNEUMONIA HERPES VIRAL
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	NECROTISING HERPETIC RETINOPATHY
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES ZOSTER OTICUS

HLGT_NAME	HLT_NAME	PT_NAME
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	MENINGITIS HERPES
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	MENINGOENCEPHALITIS HERPETIC
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	MENINGOMYELITIS HERPES
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	VARICELLA ZOSTER PNEUMONIA
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	VARICELLA ZOSTER OESOPHAGITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	VARICELLA ZOSTER GASTRITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	OPHTHALMIC HERPES ZOSTER
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	VARICELLA KERATITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	LOWER RESPIRATORY TRACT HERPES INFECTION
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HAEMORRHAGIC VARICELLA SYNDROME
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HERPES ZOSTER MENINGORADICULITIS
VIRAL INFECTIOUS DISORDERS	HERPES VIRAL INFECTIONS	HUMAN HERPESVIRUS 6 ENCEPHALITIS
VIRAL INFECTIOUS DISORDERS	POLIOMYELITIS VIRAL INFECTIONS	VACCINE ASSOCIATED PARALYTIC POLIOMYELITIS
VIRAL INFECTIOUS DISORDERS	POLYOMAVIRUS INFECTIONS	BK VIRUS INFECTION
VIRAL INFECTIOUS DISORDERS	POLYOMAVIRUS INFECTIONS	HUMAN POLYOMAVIRUS INFECTION
VIRAL INFECTIOUS DISORDERS	POLYOMAVIRUS INFECTIONS	JC VIRUS INFECTION

HLGT_NAME	HLT_NAME	PT_NAME
VIRAL INFECTIOUS DISORDERS	POLYOMAVIRUS INFECTIONS	POLYOMAVIRUS-ASSOCIATED NEPHROPATHY
VIRAL INFECTIOUS DISORDERS	POLYOMAVIRUS INFECTIONS	PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
VIRAL INFECTIOUS DISORDERS	POLYOMAVIRUS INFECTIONS	JC VIRUS GRANULE CELL NEURONOPATHY
VIRAL INFECTIOUS DISORDERS	POLYOMAVIRUS INFECTIONS	JC POLYOMAVIRUS TEST POSITIVE
VIRAL INFECTIOUS DISORDERS	POLYOMAVIRUS INFECTIONS	JC VIRUS CSF TEST POSITIVE
VIRAL INFECTIOUS DISORDERS	POLYOMAVIRUS INFECTIONS	JC POLYOMAVIRUS TEST
VIRAL INFECTIOUS DISORDERS	POLYOMAVIRUS INFECTIONS	LEUKOENCEPHALOPATHY
VIRAL INFECTIOUS DISORDERS	POLYOMAVIRUS INFECTIONS	JC POLYOMAVIRUS TEST POSITIVE

Tuberculosis PTs

HLGT_NAME	HLT_NAME	PT_NAME
BACTERIAL INFECTIOUS DISORDERS	BACTERIAL INFECTIONS NEC	ACID FAST BACILLI INFECTION
BACTERIAL INFECTIOUS DISORDERS	BACTERIAL INFECTIONS NEC	TUBERCULOUS ABSCESS CENTRAL NERVOUS SYSTEM
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	ADRENAL GLAND TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	BONE TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	BOVINE TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	CHOROID TUBERCLES
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	CONGENITAL TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	CONJUNCTIVITIS TUBERCULOUS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	CUTANEOUS TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	DISSEMINATED TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	EAR TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	EPIDIDYMITIS TUBERCULOUS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	ERYTHEMA INDURATUM
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	EXTRAPULMONARY TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	FEMALE GENITAL TRACT TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	IMMUNE RECONSTITUTION INFLAMMATORY

HLGT_NAME	HLT_NAME	PT_NAME
		SYNDROME ASSOCIATED TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	JOINT TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	LATENT TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	LUPUS VULGARIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	LYMPH NODE TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	MALE GENITAL TRACT TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	MAMMARY TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	MENINGITIS TUBERCULOUS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	OESOPHAGEAL TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	ORAL TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	PERICARDITIS TUBERCULOUS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	PERITONEAL TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	PROSTATITIS TUBERCULOUS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	PULMONARY TUBERCULOMA
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	PULMONARY TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	RENAL TUBERCULOSIS

HLGT_NAME	HLT_NAME	PT_NAME
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	SALPINGITIS TUBERCULOUS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	SILICOTUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	SPLEEN TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	THYROID TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOMA OF CENTRAL NERVOUS SYSTEM
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOSIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOSIS BLADDER
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOSIS GASTROINTESTINAL
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOSIS LIVER
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOSIS OF CENTRAL NERVOUS SYSTEM
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOSIS OF EYE
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOSIS OF GENITOURINARY SYSTEM
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOSIS OF INTRATHORACIC LYMPH NODES
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOSIS OF PERIPHERAL LYMPH NODES
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOSIS URETER
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOUS ENDOMETRITIS

HLGT_NAME	HLT_NAME	PT_NAME
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOUS LARYNGITIS
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOUS PLEURISY
MYCOBACTERIAL INFECTIOUS DISORDERS	TUBERCULOUS INFECTIONS	TUBERCULOUS TENOSYNOVITIS
EPIDERMAL AND DERMAL CONDITIONS	DERMAL AND EPIDERMAL CONDITIONS NEC	TUBERCULID
MICROBIOLOGY AND SEROLOGY INVESTIGATIONS	MYCOBACTERIA IDENTIFICATION AND SEROLOGY	TUBERCULIN TEST POSITIVE
MICROBIOLOGY AND SEROLOGY INVESTIGATIONS	MYCOBACTERIA IDENTIFICATION AND SEROLOGY	TUBERCULIN TEST FALSE NEGATIVE
MICROBIOLOGY AND SEROLOGY INVESTIGATIONS	MYCOBACTERIA IDENTIFICATION AND SEROLOGY	MYCOBACTERIUM TUBERCULOSIS COMPLEX TEST POSITIVE

Autoimmune Disorders PTs

Thyroiditis, autoimmune diabetes, uveitis, psoriasis, IBD, celiac disease, demyelination, and SLE.

HLGT_NAME	HLT_NAME	PT_NAME
ENDOCRINE INVESTIGATIONS (INCL. SEX HORMONES)	THYROID ANALYSES	ANTI-THYROID ANTIBODY
ENDOCRINE INVESTIGATIONS (INCL. SEX HORMONES)	THYROID ANALYSES	ANTI-THYROID ANTIBODY POSITIVE
ENDOCRINE INVESTIGATIONS (INCL. SEX HORMONES)	THYROID ANALYSES	THYROID STIMULATING IMMUNOGLOBULIN
ENDOCRINE INVESTIGATIONS (INCL. SEX HORMONES)	THYROID ANALYSES	THYROID STIMULATING IMMUNOGLOBULIN INCREASED
HLGT AUTOIMMUNE DISORDERS	HLT ENDOCRINE AUTOIMMUNE DISORDERS	AUTOIMMUNE HYPOTHYROIDISM
HLGT AUTOIMMUNE DISORDERS	HLT ENDOCRINE AUTOIMMUNE DISORDERS	AUTOIMMUNE THYROID DISORDER
HLGT AUTOIMMUNE DISORDERS	HLT ENDOCRINE AUTOIMMUNE DISORDERS	SILENT THYROIDITIS
HLGT AUTOIMMUNE DISORDERS	HLT ENDOCRINE AUTOIMMUNE DISORDERS	BASEDOW'S DISEASE
HLGT AUTOIMMUNE DISORDERS	HLT ENDOCRINE AUTOIMMUNE DISORDERS	HASHITOXICOSIS
HLGT AUTOIMMUNE DISORDERS	HLT ENDOCRINE AUTOIMMUNE DISORDERS	ATROPHIC THYROIDITIS
HLGT AUTOIMMUNE DISORDERS	HLT ENDOCRINE AUTOIMMUNE DISORDERS	AUTOIMMUNE THYROIDITIS
HLGT AUTOIMMUNE DISORDERS	HLT ENDOCRINE AUTOIMMUNE DISORDERS	AUTOIMMUNE THYROID DISORDER
HLGT AUTOIMMUNE	HLT ENDOCRINE	AUTOIMMUNE

HLGT_NAME	HLT_NAME	PT_NAME
DISORDERS	AUTOIMMUNE DISORDERS	HYPOTHYROIDISM
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	IMMUNE-MEDIATED THYROIDITIS
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	IMMUNE-MEDIATED HYPERTHYROIDISM
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	IMMUNE-MEDIATED HYPORTHYROIDISM
HLGT AUTOIMMUNE DISORDERS	ENDOCRINE AUTOIMMUNE DISORDERS	TYPE 1 DIABETES MELLITUS
HLGT AUTOIMMUNE DISORDERS	ENDOCRINE AUTOIMMUNE DISORDERS	FULMINANT TYPE 1 DIABETES
HLGT AUTOIMMUNE DISORDERS	AUTOIMMUNE DISORDERS NEC	AUTOIMMUNE UVEITIS
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	IMMUNE- MEDIATED UVEITIS
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	UVEITIS
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	DERMATITIS PSORIASIFORM
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	ERYTHRODERMIC PSORIASIS
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	GUTTATE PSORIASIS
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	NAIL PSORIASIS
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	PSORIASIS
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	PUSTULAR PSORIASIS
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	REBOUND PSORIASIS

HLGT_NAME	HLT_NAME	PT_NAME
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	PARADOXICAL PSORIASIS
HLGT GASTROINTESTINAL INFLAMMATORY CONITIONS	HLT COLITIS (EXCL. INFECTIVE)	INFLAMMATORY BOWEL DISEASE
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	COLITIS ULCERATIVE
HLGT IMMUNE DISORDERS NEC	HLT IMMUNE AND ASSOCIATED CONDITIONS NEC	CROHN'S DISEASE
HLGT AUTOIMMUNE DISORDERS	AUTOIMMUNE DISORDERS NEC	CELIAC DISEASE
SMQ DEMYELINATION (NARROW)		
SMQ SYSTEMIC LUPUS ERYTHEMATOSUS (NARROW)		

15. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres
for Pharmacoepidemiology
and
Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on
15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices.

Study title: An observational post-approval safety study of golimumab in treatment of polyarticular Juvenile Idiopathic Arthritis (pJIA) using the German Biologics JIA Registry (BiKeR)

EU PAS Register® number: EUPAS20781
Study reference number (if applicable): RRA-20171

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Progress report(s)	☒	☐	☐	5
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

1.1.4. This study has annual progress reports and final report. Interim report is not planned.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

Section 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)	☒	☐	☐	8.1; 8.2
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2; 8.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.7.1
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))	☒	☐	☐	8.7.2
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)	☒	☐	☐	10

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.1.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.1.1; 8.2.1; 8.2.2.1
	4.2.2 Age and sex	☒	☐	☐	8.1.1; 8.2.2
	4.2.3 Country of origin	☒	☐	☐	8.1.1
	4.2.4 Disease/indication	☒	☐	☐	8.1.1; 8.2.2
	4.2.5 Duration of follow-up	☒	☐	☐	8.2.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.2.2; 8.3.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	8.3.2
5.3	Is exposure categorised according to time windows?	☒	☐	☐	8.3.2
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.2.2; 8.7.2

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.3
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.3
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)	☒	☐	☐	8.1.1; 8.3.3
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)	☒	☐	☐	8.3.4.1; 8.7.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.7; 8.9

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)	☒	☐	☐	8.1.1; 8.3.2
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.1.1; 8.3.3
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.1.1; 8.3.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.1.1; 8.3.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.1.1; 8.3.3

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)	☒	☐	☐	8.1.1; 8.3.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.3.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.3.3; 14.1
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.3.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.5
10.3 Are descriptive analyses included?	☒	☐	☐	8.7.1
10.4 Are stratified analyses included?	☒	☐	☐	8.7.1; 8.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.2.1
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.7.2

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)	☒	☐	☐	8.1.1; 8.8
11.2 Are methods of quality assurance described?	☒	☐	☐	8.1.1; 8.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

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?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	8.7.2.1; 8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.1.1

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?	☒	☐	☐	8.1.1; 9
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	8.1.1; 9
13.3 Have data protection requirements been described?	☒	☐	☐	8.1.1; 9

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?	☒	☐	☐	4

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)?	☒	☐	☐	5; 11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

SPONSOR'S RESPONSIBLE PARTY SIGNATURE AND PARTICIPATING PHYSICIAN AGREEMENT

Protocol PCSIMMA0237

SPONSOR'S RESPONSIBLE PARTY SIGNATURE AND PARTICIPATING PHYSICIAN AGREEMENT

Sponsor's Responsible Party (Main Author):

Name (typed or printed): PPD PhD

Institution: PPD

Signature: _____ Date: _____

Participating Physician Agreement:

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Principal Participating Physician:

Name (typed or printed): Dr Gerd Horneff, Professor

Institution and Address: PPD

Telephone Number: PPD

Signature: PPD Date: PPD

(Day Month Year)

Note: If the address or telephone number of the participating physician changes during the study, written notification will be provided to the sponsor; a protocol amendment will not be required.

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Status: Approved, Date: 24 January 2025

SPONSOR'S RESPONSIBLE PARTY SIGNATURE

Sponsor's Responsible Party (Main Author):

Name (typed or printed): PPD PhD

Institution: PPD

Signature: electronic signature appended at the end of this document Date: electronic signature appended at the end of this document

Participating Physician Agreement:

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Principal Participating Physician:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Note: If the address or telephone number of the participating physician changes during the study, written notification will be provided to the sponsor; a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	31-Jul-2025 09:26:28 (GMT)	Document Approval
PPD	31-Jul-2025 10:05:24 (GMT)	Document Approval
PPD	31-Jul-2025 10:09:47 (GMT)	Document Approval
PPD	31-Jul-2025 10:09:48 (GMT)	Document Approval