# NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY PROTOCOL

| | | | |
|---|---|---|---|
| Project Number: | GLPG0634 | | |
| Study Number: | GLPG0634-CL-403 | | |
| Study Title: | Non-interventional post-authorization safety study of filgotinib in the treatment of patients with moderate to severe active rheumatoid arthritis within European registries | | |
| Development Phase: | 4 | | |
| Status: | Final | | |
| Version: | 1.0 | Date: | 20-Jan-2022 |
| EU PAS Register No: | To be determined | ClinicalTrials.gov identifier: | Not applicable |
| Active Substance | Filgotinib (ATC code: L04AA45) | | |
| Medicinal Product | Jyseleca® (filgotinib) | Product Reference | EU/1/20/1480 |
| Procedure Number | EMEA/H/C/005113/MEA/002-006 | | |
| Joint PASS | No | | |
| Research Question and Objectives | To evaluate the incidence rates of infections, malignancy, cardiovascular, and other safety endpoints of interest in patients with rheumatoid arthritis initiating treatment with filgotinib. For context, incidence rates will also be calculated in comparator cohorts. | | |
| Country (-ies) of study | Denmark, Germany, Sweden, Spain, United Kingdom | | |
| Author/ Contact person | Name: PPD<br>Email: PPD | | |
| Marketing Authorization Holder | Galapagos NV<br>Generaal De Wittelaan L11 A3 | | |

| | |
|---|---|
| | 2800 Mechelen<br>Belgium |
| MAH contact person | Name: PPD<br>Email: PPD |

**Confidentiality Statement**

# TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES



## LIST OF ANNEXES

# 1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ACR | American College of Rheumatology |
| ADR | adverse drug reaction |
| AE | adverse event |
| ARTIS | Anti-Rheumatic Treatment in Sweden |
| AS | ankylosing spondylitis |
| bDMARD | biologic disease-modifying antirheumatic drug |
| BIOBADASER | Spanish Registry of Adverse Events of Biological Therapies in Rheumatoid Diseases (Registro Español de Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas) |
| BSRBR-RA | British Society for Rheumatology Biologics Register-Rheumatoid Arthritis |
| csDMARD | conventional synthetic disease-modifying antirheumatic drug |
| CRP | C-reactive protein |
| DAS28 | Disease Activity Score for 28 Joint Count |
| DANBIO | Danish Nationwide Clinical Register for Patients with Rheumatoid Arthritis |
| DMARD | disease-modifying antirheumatic drug |
| DRFZ | Deutsches Rheuma Forschungszentrum (German Rheumatism Research Centre) |
| DVT | deep venous thromboembolism |
| EMA | European Medicines Agency |
| ESR | erythrocyte sedimentation rate |
| EU | European Union |
| GI | gastrointestinal |
| GLPS | Global Patient Safety |
| Gilead | Gilead Sciences |
| GVP | Good Pharmacovigilance Practices |
| HAQ | Health Assessment Questionnaire |
| Hb | hemoglobin |
| HDL | high-density lipoprotein |
| HMA | Heads of Medicines Agencies |
| ICD | International Classification of Diseases |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| JAK | Janus kinase |
| MACE | major adverse cardiovascular events |
| MAH | marketing authorization holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MPA | Medical Products Agency |
| NICE | National Institute for Health and Clinical Excellence |

| | |
|---|---|
| NMSC | nonmelanoma skin cancer |
| PASS | post-authorization safety study |
| PE | pulmonary embolism |
| PY | person-year |
| QPPV | Qualified Person for Pharmacovigilance |
| RA | rheumatoid arthritis |
| RABBIT | Rheumatoide Arthritis: Beobachtung der BiologikaTherapie (Rheumatoid Arthritis: Observation of Biologic Therapy) |
| RCT | randomized clinical trial |
| RF | rheumatoid factor |
| RMP | risk management plan |
| RR | relative risk |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | statistical analysis software |
| SOP | standard operating procedure |
| SRQ | Swedish Rheumatology Quality Register |
| STATs | signal transducer and activator of transcription |
| tsDMARD | targeted synthetic disease-modifying antirheumatic drug |
| UK | United Kingdom |
| US, USA | United States, United States of America |
| VAS | visual analog scale |
| VTE | venous thromboembolism |

# 3. RESPONSIBLE PARTIES

**Table 1 Table of Responsible Parties**

| Responsibility | Name, Title, Qualifications, Affiliation, Address | Contact Information |
|---|---|---|
| Marketing Authorization Holder | Galapagos NV<br>Generaal De Wittelaan L11 A3<br>2800 Mechelen<br>Belgium | PPD<br>PPD |
| Epidemiology Leader | PPD | PPD |
| ARTIS Principal Investigator | PPD | PPD |
| BIOBADASER Principal investigator | PPD | PPD |
| BSRBR-RA Principal Investigator | PPD | PPD |
| DANBIO Principal Investigator | PPD | PPD<br>PPD |

| | | |
|---|---|---|
| | PPD | |
| RABBIT Principal Investigators | PPD | PPD |
| Pharmacovigilance | PPD | PPD |
| EU&UK QPPV | PPD | PPD |

# 4. ABSTRACT

**Study Title:** Non-interventional post-authorization safety study of filgotinib in the treatment of patients with moderate to severe active rheumatoid arthritis within European registries

**Protocol version:** 1.0
**Date:** 20-Jan-2022
**Author, Affiliation:** PPD

**Rationale and Background:**
Filgotinib is a Janus kinase (JAK) 1 preferential inhibitor for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Randomized clinical trials (RCTs) have provided information on filgotinib's efficacy and safety (Combe et al., 2021; Genovese et al., 2019; Westhovens et al., 2021). Assessment of safety using RCT data, however, is subject to limitations, such as relatively small sample sizes, certain inclusion and exclusion criteria, and limited duration of follow-up. Long-term safety data are needed in patients treated with filgotinib in real-world clinical settings and in patient populations where there are limited RCT data. Several disease-based prospective rheumatology registries have been established in Europe to evaluate the safety profiles (including rates of infections) (Askling et al., 2007; Galloway et al., 2011; Rutherford, Subesinghe, Hyrich, & Galloway, 2018; Strangfeld et al., 2009), malignancy (Askling et al., 2009; Mercer et al., 2015), major adverse cardiovascular events (MACE) (Ljung, Askling, Rantapää-Dahlqvist, Jacobsson, & ARTIS Study Group, 2014; Low et al., 2017; Meissner et al., 2017), risk of venous thromboembolism [VTE] (Davies et al., 2011; Holmqvist et al., 2012) and mortality (Listing et al., 2015; Simard et al., 2012) of new biologic, biosimilar, or other advanced targeted therapies and have been used extensively to address post-authorization safety requirements. They also offer the possibility of comparative analyses with comparator groups.

The purpose of this non-interventional post-authorization safety study is to evaluate the long-term safety of filgotinib in the treatment of patients with moderate to severe, active RA by making secondary use of data collected by European registries including the Anti-Rheumatic Treatment in Sweden (ARTIS) register, the Spanish Registry of Adverse Events of Biological Therapies in Rheumatoid Diseases (BIOBADASER), the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA), the Danish Nationwide Clinical Register for Patients with Rheumatoid Arthritis (DANBIO), and the German registry Rheumatoide Arthritis: Beobachtung der BiologikaTherapie (RABBIT).

**Research Question and Objectives**

**Objectives**

***Primary***

- To estimate incidence rates of the following important, identified, and potential risks listed in the risk management plan (RMP): serious and opportunistic infections, Herpes zoster and primary Varicella infection, MACE, VTE (including deep venous thrombosis [DVT], pulmonary embolism [PE]), hyperlipidemia, malignancy, non-melanoma skin cancer (NMSC), and gastrointestinal (GI) perforation as well as all-cause mortality in RA patients in Denmark, Germany, Sweden, Spain, and the United Kingdom (UK) who initiate treatment with filgotinib.

***Secondary***

- To describe patients' baseline characteristics including risk factors associated with the development of the above-mentioned endpoints.

| |
|---|
| – To estimate incidence rates of the endpoints mentioned above in comparator cohorts provided by each registry in order to provide context for incidence rates observed in patients treated with filgotinib.<br>– To compare incidence rates of the above-mentioned endpoints between patients treated with filgotinib and patients in comparator cohorts (depending on statistical power and comparability between the filgotinib cohort and the comparator cohort in relation to their underlying risk of outcome development).<br>– To estimate incidence rates of the abovementioned safety endpoints in very elderly patients (>= 75 years) (depending on data availability). |
| **Study design:**<br><br>Non-interventional post-authorization safety prospective cohort study that will be conducted by making secondary use of data collected by European registries including the ARTIS registry in Sweden, BIOBADASER in Spain, the BSRBR-RA in the UK, the DANBIO registry in Denmark, and the RABBIT registry in Germany. |
| **Population:**<br><br>The study population will include RA patients in each country who initiate treatment with filgotinib and are enrolled in the respective registry, following approval in Europe and commercial availability for the treatment of RA in each country until the end of the study period. Overall study duration will be 8 years after the first patient is enrolled, and it will include all available follow-up time for the included patients. To provide context for the incidence rates of the safety endpoints observed in patients initiating treatment with filgotinib, comparator cohorts of patients within the registry will also be used. |
| **Variables:**<br><br>The study will include baseline and follow-up data (including clinical, demographic, and patient characteristics, comorbidities and risk factors associated with the development of the endpoints mentioned above, current, and previous therapies) as well as data on safety endpoints as collected by each registry. |
| **Data Source:**<br><br>The study will be conducted within each registry using its data sources. |
| **Study Size:**<br><br>This is a descriptive study without prespecified hypotheses. All eligible patients in each registry will be included and no upper limit on the sample size is defined. The study size target with respect to filgotinib exposure is 500 patients in each registry. However, this will depend on use of filgotinib in the respective country, which is likely to be a good measure of exposure overall in a given subpopulation and therefore provide information of public health interest.<br><br>The ability to perform comparative analyses on the incidence rates of safety endpoints between RA patients initiating filgotinib and patients in comparator cohorts will depend on statistical power and comparability between the filgotinib cohort and the comparator cohort in relation to their underlying risk of outcome development.<br><br>Assuming an average follow-up of 3 years and a risk rate of approximately 40/1000 person-years (PYs) (e.g, rate for serious infections) (Askling et al., 2007; Galloway et al., 2011; Rutherford et al., 2018), |

a sample size of 500 patients exposed to filgotinib and 2000 patients exposed to biologic disease-modifying antirheumatic drugs (bDMARDs) would be sufficiently powered (>80%) for detection of a 50% difference in rates between filgotinib-exposed patients and bDMARD-exposed patients. For an endpoint with a rate of 10/ 1000 PY (eg, malignancy (Askling et al., 2009; Mercer et al., 2015), 500 filgotinib-exposed patients and 2000 bDMARD-exposed patients would provide enough power (>80%) to detect a 2-fold difference between the rates observed in patients on filgotinib and patients on bDMARDs. For MACE and VTE with an estimated rate of approximately 5/ 1000 PY (Davies et al., 2011; Ljung et al., 2014; Low et al., 2017), a sample size of 500 filgotinib-exposed patients and 2000 bDMARD-exposed patients would be required for the detection of a 2.5-fold difference between the rates of the 2 arms with 80% power.

Any increase in the numbers of patients exposed to filgotinib or in the average follow-up duration would result in increased power to detect a difference in the observed rates between the filgotinib cohort and the comparator cohort.

**Data Analysis:**

All statistical analyses will be performed by each registry.

Regular reports adhering to a predefined format will be provided by each registry to the marketing authorization holder (MAH) at 6-month or 12-month intervals after enrolment is opened to filgotinib-treated patients in participating countries.

The final analysis will be conducted at the end of the study period and will summarize descriptive statistics for patients initiating filgotinib (in all patients and in subgroups defined by baseline characteristics [depending on sufficient sample size]) as well as for patients in the comparator cohorts. Number of events and crude incidence rates, derived from registry linkages, will be tabulated for each cohort and safety endpoint of interest.

Depending on adequate statistical power and comparability between the filgotinib cohort and the comparator cohort in relation to their underlying risk of outcome development, comparative analysis between patients exposed to filgotinib and patients in the comparator cohort adjusted for potential confounders will be performed in the final analysis.

Detailed information on the analyses will be provided in the statistical analysis plans.

**Safety Reporting:**

This study will make secondary use of data collected by ARTIS, BIOBADASER, BSRBR-RA, DANBIO, and RABBIT registries. Aggregate safety data from regular reports will be provided to the MAH by the registry at regular time intervals and will be included in regulatory updates (i.e., periodic benefit-risk evaluation reports/ periodic safety update reports) and considered in light of signal detection.

**Milestones:**

Data collection and study report milestones are based on assumptions of commercial availability of filgotinib.

Study reports may also be used in regulatory communications in other countries for contextualization purposes. Scientific manuscripts based on specific safety events may be developed for external publication purposes.

| Milestone | Date Planned |
|---|---|
| Registration in EU PAS register | Within 4 months after protocol approval |
| Start of data collection (last registry) [1,2] | Q2 2022 |
| End of data collection (expected) | Q2 2030 |
| Interim reports | Every 2 years |
| Final report submission | Q2 2031 |

EU = European Union; PAS = post-authorization study; Q1 = first quartile; Q2 = second quartile; Q4 = fourth quartile.
[1]Expected date of the last registry to include the first patient initiating filgotinib
[2] Patients may be entered into the registry prior to protocol finalization as the data fields are fixed by the registry.

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPP) and Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

# 5. AMENDMENTS AND UPDATES

None.

# 6. MILESTONES

The milestones for the study are presented below in Table 2. To supply a consolidated report, the submission of the reports (interim and final) to the regulator will be arranged once results have been supplied to the MAH from all participating registries. The start of data collection is the date at which the first patient in each registry is administered filgotinib. Prospective data collection for each registry is intended to last for 8 years following the start date. Therefore, the overall study (all registries) would complete data collection 8 years after the last registry's start of data collection. From current projections of commercial availability and reimbursement, the last registry to start data collection would likely be in Q2 2022 and thus all data collection should be complete by Q2 2030. However, for the registries that rely on data linkage (Anti-Rheumatic Treatment in Sweden [ARTIS], Danish Nationwide Clinical Register for Patients with Rheumatoid Arthritis [DANBIO]) it may not be possible to obtain precisely 8 years of follow-up as this depends on the timing of the linkage (e.g., for ARTIS the linked data is currently updated every 2 years and for DANBIO a similar delay may occur), which may occur before the 8-year mark.

**Table 2 Milestones**

| Milestone | Planned Date |
|---|---|
| Start of Data Collection (last registry[1,2]) | Q2 2022 |
| End of Data Collection (expected) | Q2 2030 |
| Interim Reports | Every 2 years |
| Registration in the EU PAS register | Within 4 months after protocol approval |
| Final Report of Study Results | Q2 2031 |

EU = European Union; PAS = post-authorization study; Q1 = first quartile; Q2 = second quartile; Q4 = fourth quartile.
[1] Expected date of the last registry to include the first patient initiating filgotinib
[2] Patients may be entered into the registry prior to protocol finalization as the data fields are fixed by the registry

If any registries were unable to provide the agreed reports (e.g. due to unavailability of filgotinib-exposed patients, local regulatory changes, etc.), the combined results from the other participating registries will be provided following the milestone schedule, and any missing information will be provided within the overall study period if made available by the registry(s).

# 7. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease with an estimated prevalence of 0.4% to 1.0% and a mean annual incidence of 0.02% to 0.05% in Europe and North America (Alamanos et al., 2006). Although people of any age can be affected, the onset of RA is most frequent between the ages of 40 and 50 years, and women are affected 3-times more often than men (Cross et al., 2014). The pathogenesis of RA consists of genetic and environmental factors that lead to a chronic inflammatory response targeting synovial tissue of the joints and may result in marked destruction and deformity of joints, with considerable pain, disability, and impact on quality of life (Firestein & McInnes, 2017; Smolen et al., 2016; Sokka et al., 2010). RA patients experience various comorbidities including infections, cardiovascular diseases (Chung et al., 2014; Lindhardsen et al., 2012), and malignancies (Simon et al., 2015), which may be in addition to, or further worsened by treatment side effects.

Filgotinib is an adenosine triphosphate-competitive and reversible Janus kinase (JAK) 1 preferential inhibitor. JAKs are intracellular enzymes that transmit signals arising from cytokine or growth-factor receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis, cytokine signaling, and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) that modulate intracellular activity including gene expression. Filgotinib modulates the signaling pathway by attenuating the phosphorylation and activation of STATs.

Jyseleca® (filgotinib) was approved in the European Union (EU) in September 2020 and is indicated for the treatment of moderate to severe active RA in adult patients who have responded

inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Jyseleca® may be used as monotherapy or in combination with methotrexate. The recommended dose of filgotinib for adult patients with RA is 200 mg once daily. A dose of 100 mg once daily is recommended for patients with moderate or severe renal impairment (creatinine clearance 15 to < 60 mL/min). A starting dose of 100 mg once daily is recommended for patients aged >= 75 years.

Randomized clinical trials (RCTs) have provided information on filgotinib's efficacy and safety (Combe et al., 2021; Genovese et al., 2019; Westhovens et al., 2021). Assessment of safety using RCT data, however, is subject to limitations, such as the relatively small sample sizes, certain inclusion and exclusion criteria, and limited duration of follow-up. Long-term safety data are needed of patients treated with filgotinib in real-world clinical settings and in patient populations where there are limited RCT data. Several disease-based prospective rheumatology registries have been established in Europe to evaluate the safety profiles, including rates of infections (Askling et al., 2007; Galloway et al., 2011; Rutherford et al., 2018; Strangfeld et al., 2009), malignancy (Askling et al., 2009; Mercer et al., 2015), major adverse cardiovascular events [MACE] (Ljung et al., 2014; Low et al., 2017; Meissner et al., 2017), risk of venous thromboembolism [VTE] (Davies et al., 2011; Holmqvist et al., 2012) and mortality (Listing et al., 2015; Simard et al., 2012) of new biologic, biosimilar or other advanced targeted therapies and have been used extensively to address post-authorization safety requirements. They also offer the possibility of comparative analyses with comparator groups.

The purpose of this non-interventional post-authorization safety study (PASS) is to evaluate the long-term safety of filgotinib in the treatment of patients with moderate to severe active RA within European registries including the ARTIS register, the Spanish Registry of Adverse Events of Biological Therapies in Rheumatoid Diseases (BIOBADASER), the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA), the Danish Nationwide Clinical Register for Patients with Rheumatoid Arthritis (DANBIO), and the German registry Rheumatoide Arthritis: Beobachtung der BiologikaTherapie (RABBIT). This PASS is being conducted by the marketing authorization holder (MAH) as a Category 3 commitment to the European Medicines Agency (EMA) and to the Medicines and Healthcare products Regulatory Agency (MHRA).

# 8. RESEARCH QUESTION AND OBJECTIVES

**Objectives**

Primary

- To estimate incidence rates of the following important identified and potential risks listed in the risk management plan (RMP): serious and opportunistic infections, Herpes zoster and primary Varicella infection, MACE, VTE (including deep venous thromboembolism [DVT], pulmonary embolism [PE]), hyperlipidemia, malignancy, nonmelanoma skin cancer (NMSC), and gastrointestinal (GI) perforation as well as all-cause mortality in RA patients in Denmark, Germany, Sweden, Spain, and the United Kingdom (UK) who initiate treatment with filgotinib.

Secondary

- To describe patients' baseline characteristics including risk factors associated with the development of the above-mentioned endpoints.
- To estimate incidence rates of the endpoints mentioned above in comparator cohorts provided by each registry in order to provide context for incidence rates observed in patients treated with filgotinib.
- To compare incidence rates of the above-mentioned endpoints between patients treated with filgotinib and patients in comparator cohorts (depending on statistical power and comparability between the filgotinib cohort and the comparator cohort in relation to their underlying risk of outcome development).
- To estimate incidence rates of the above-mentioned safety endpoints in very elderly patients (>=75 years) (depending on data availability).

# 9. RESEARCH METHODS

## 9.1. Study Design

Non-interventional post-authorization safety prospective cohort study that will be conducted by making secondary use of data collected by European registries including the ARTIS registry in Sweden, BIOBADASER in Spain, the BSRBR-RA in the UK, the DANBIO registry in Denmark, and the RABBIT registry in Germany.

The study population will include all RA patients who initiate treatment with filgotinib and are enrolled in each registry, following approval in Europe and commercial availability in the respective country until the end of study period. The overall study duration in each registry will be 8 years after the first patient is enrolled in the registry, and it will include all follow-up time for the included patients. To provide context for the incidence rates of the safety endpoints observed in patients initiating treatment with filgotinib, comparator cohorts of patients within each registry will also be used.

The study will aim to minimize bias by using data from high quality registries that have been used for similar safety studies before, by including contemporaneous comparator cohorts, and by use of propensity score techniques to address confounding.

## 9.2. Setting

### 9.2.1. ARTIS

Sweden is a Scandinavian country with 9.7 million inhabitants. The prevalence of RA in Sweden is around 0.7% and the overall incidence is around 40/100 000 per year (Jonas K. Eriksson et al., 2013; Martin Neovius et al., 2011).

Swedish healthcare is tax-funded and offers universal access. Hospital referral is based on geography rather than insurance status. Patients with RA are typically treated by rheumatologists, the vast majority of whom work in public and hospital-based clinics.

Health and demographic information are collected in a series of registers with a high degree of completeness resulting from the mandatory and semi-automated registration of their data. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born/ immigrated thereafter, linkage of data from different registries is possible (Ludvigsson et al., 2009). The registries are maintained by governmental bodies (the main registries used in this project are held by the National Board of Health and Welfare [Socialstyrelsen] and Statistics Sweden), who may perform data linkages and provide de-identified data for research purposes.

Use of biologic and other targeted RA treatments in Sweden has never been subject to any formal approvals (except for a period during 2002 to 2003, when manufacturing issues led to reduced availability of etanercept), mandatory treatment histories, or disease activity indices. Instead, the Swedish Society for Rheumatology has issued guidelines for the use of biologics, which are revised on an annual basis, but the ultimate decision to treat with biologics is and has always resided with the treating rheumatologist.

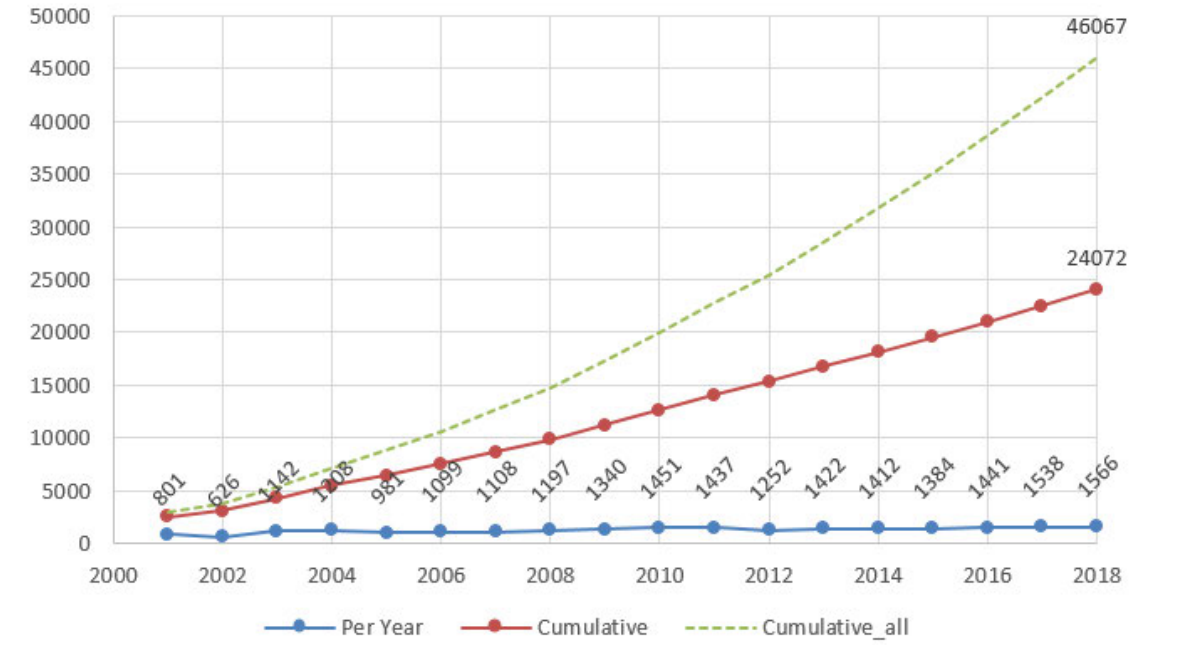
**The Swedish Rheumatology Quality Register and ARTIS Registries**

The Swedish Rheumatology Quality Registry (SRQ) was started in 1995 by the Swedish Society of Rheumatology to improve the healthcare and treatment for patients with RA (J. K. Eriksson et al., 2014). SRQ followed on regional registry initiatives to enable a national real-world documentation of many different aspects of RA and developed over time into a harmonized national registry. SRQ was started mainly for patients with RA, but over time it has been expanded to cover several other rheumatic diseases including ankylosing spondylitis, psoriatic arthritis, myositis, and systemic lupus erythematosus. Initially focusing on early RA, SRQ has gradually come to include also other segments. Currently, SRQ encompasses data on approximately 80% of all patients with RA seen in Rheumatology.

Since 1999, ARTIS has been running a safety surveillance database for immunomodulators as part of SRQ, including all presently available and new therapies used for the treatment of patients with inflammatory rheumatic diseases. It covers approximately 90% of all biologic initiations in Sweden after 1999 (M. Neovius et al., 2011; Wadström et al., 2015).

To maintain this high percentage and further improve completeness, the Swedish Society for Rheumatology regularly holds scientific meetings to present surveillance data. The registry managers and research nurses regularly visit participating centers to support the clinicians in managing the web-based forms and/ or entering information. In each of the 6 geographical regions, at least 1 rheumatologist is assigned as responsible for registration. These rheumatologists are included in the ARTIS steering committee.

By June 2017, the follow-up within ARTIS included more than 40000 patients (65% women) and more than 80000 biologic treatment initiations. Mean age at start of biologic treatment is approximately 50 years. The treatment indication is RA or polyarthritis among 52% of the patients. Figure 1 depicts the accumulated number of patients, and Figure 2 shows the total number of treatment episodes and their distribution across specific drugs.




Dashed line:number of patients across all rheumatology indications; bold lines: number of patients withRA.

**Figure 1 Accumulated Number of First-ever Biologic Initiations Registered in the Swedish Rheumatology Quality Register**

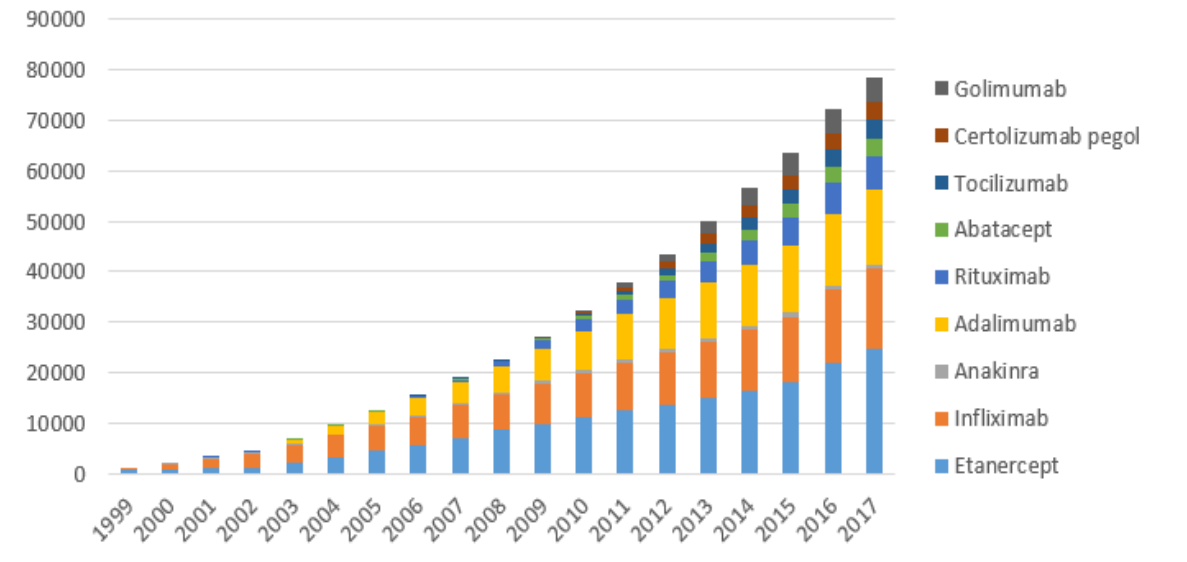



**Figure 2 Cumulative Number of Treatment Initiations in the Swedish Follow-up on Biologics Treatment Among Patients with Rheumatic Diseases**

ARTIS is designed to assist in signal detection (through facilitated reporting and contextualization of adverse drug reactions [ADRs]), signal evaluation (through registry linkage - based evaluations of putative adverse outcomes), and for the short- and long-term evaluation of

drug safety and changes in comorbidity patterns via biologic, biosimilar, and targeted therapies (through comparative analyses of risks and determinants for comorbidities and safety outcomes based on linkage data). Accordingly, safety data from the ARTIS program come from 2 sources:

1. Spontaneous ADR reporting to the Medical Products Agency (MPA). These ADRs are summarized in semi-annual reports adhering to a predefined format (Annex 3).
2. Data from SRQ/ARTIS are (on a regular basis) linked to data from other national Swedish registries.

### 9.2.2. BIOBADASER

BIOBADASER is a prospective follow-up study assessing the long-term safety of biologic, biosimilar, and other targeted treatments in patients with rheumatic diseases. BIOBADASER was created by the Spanish Society of Rheumatology (Sociedad Española de Reumatología,) and the Spanish Agency of Medicines and Medical Devices (Agencia Española del Medicamento y Productos Sanitarios) in 2000 and continued with Phase II in 2006 aiming to collect information on the safety and adverse events (AEs) in patients who had begun biologic treatment (L. Carmona et al., 2005). BIOBADASER helped to establish the relationship between the tumor necrosis factor inhibitor agents and the reactivation of latent tuberculosis in patients with rheumatic diseases (Loreto Carmona et al., 2005; Gómez-Reino et al., 2003, 2007). The appearance of biosimilars and targeted synthetic drugs, and the need expressed by regulatory agencies to assess the effectiveness and safety of these agents in daily clinical practice, together with changes in regulation and legislation in pharmacovigilance, determined the launch of the BIOBADASER Phase III in December 2015 (Sanchez-Piedra et al., 2019).

The objectives for BIOBADASER Phase III are:

- To identify significant AEs occurring during treatment of rheumatic diseases with biologic, biosimilar, and other targeted therapies and estimate their frequency of occurrence.
- To identify unexpected AEs.
- To identify significant AEs occurring after discontinuation of treatment.
- To evaluate, under nonexperimental conditions, the elapsed time until discontinuation of biologic, biosimilar, and other targeted therapies in patients suffering from any rheumatic pathology, as well as the reasons for this interruption (secondary effects, ineffectiveness or loss of the biologic effectiveness, remission, or death).
- To evaluate changes in disease activity of patients enrolled in the registry.

During the first year of Phase III, 35 centers across Spain participated. Starting in the second year, a maximum of 20 centers that met the quality standards (including being amongst the 20 best recruiters, collaborating in the online monitoring of the registry, and having less than 25% failures in monitoring) remained in the registry. As of today, there are 28 participating centers meeting the quality standards.

Approximately 40% of patients enrolled in the registry have a diagnosis of RA. Patients eligible for enrolment in BIOBADASER Phase III are:

- Patients with RA diagnosis who start treatment (or are under treatment) with biologic therapy (except infliximab, etanercept, and adalimumab), biosimilar, or targeted synthetic treatment at a participating center
- Patients with any other diagnosis who start treatment (or are under treatment) with biologic, biosimilar, or targeted therapy at a participating center
- Patients who are being treated with biologics or have had treatment suspended, for any reason, provided that no more than 1 year has passed since they last received treatment and that all the necessary data are available for recording (concerning the patient, treatment, and AEs)
- Patients who authorize the prospective collection of data in accordance with the formula indicated on the informed consent form

### 9.2.3. BSRBR-RA

BSRBR-RA is an ongoing prospective observational cohort study that was established in 2001 in the UK. The primary aim of BSRBR-RA is to study the long-term safety of biologic and other targeted therapies in patients with RA. For the first 7 to 8 years, the main focus was on the study of the safety profile of the first 3 tumor necrosis factor inhibitor (TNFi) agents (i.e, adalimumab, etanercept, and infliximab) as a class and as individual therapies. With the exception of the risk of developing tuberculosis, BSRBR-RA has not demonstrated any clear differences in AE profiles between these agents. At the time, the most appropriate comparison group for these 3 TNFi agents was patients with active RA receiving treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

Several new biologic, biosimilar, and other targeted therapies have since been developed and are receiving National Institute for Health and Clinical Excellence (NICE) approval. Some of these drugs are being used after TNFi therapy and some are proposed for first-line use following csDMARD failure. These agents are all targeted therapies and act on cells, cytokines, or other pathways that play a key role in inflammation and the functioning of the immune system. With each new agent there has to be concern as to what the safety profile may be in routine clinical use. There is an increased risk of premature mortality, serious infection, cardiovascular disease, and lymphoproliferative malignancy in patients with RA and other connective tissue diseases, independent of the treatment they have received. Thus, the patients most likely to receive these new therapies are already at increased risk of adverse outcomes.

Additionally, it is fundamentally important not just to document the occurrence of these events in a treated cohort of patients, but to compare their occurrence with that which might have occurred

if such patients had remained on "conventional" therapy or received a different biologic, biosimilar, or other targeted therapy. Within the BSRBR-RA there are 2 comparator cohorts. The first comparator cohort includes patients with active RA registered to the BSRBR-RA within 6 months of their first exposure to an established TNFi agent (ie, adalimumab, etanercept, or infliximab). Recruitment to this cohort started in 2010 and is ongoing. For analyses, patients who switch to a second biologic or other targeted therapy will have their follow-up censored at the time of switching treatments. They will then be eligible to enter the filgotinib cohort if they go on to be treated with filgotinib.

The second comparator cohort is a historic RA cohort of patients with prevalent active RA (disease activity score DAS-28 [DAS28] >= 4.2) treated with csDMARDs recruited to BSRBR-RA from a select number of sites within the UK between 2002 and 2008 for whom follow-up data are already available. Patients who subsequently progress to a biologic, biosimilar, or other targeted therapy will, for the purpose of analysis, have their follow-up censored at the time of the first dose, thus they will contribute patient months of follow-up prior and up to the treatment change date. They will then be eligible to enter the filgotinib- or biologic disease-modifying antirheumatic drug (bDMARD)-exposed cohort.

The British Society for Rheumatology treatment guidelines recommend that all patients receiving biologic, biosimilar, or other new targeted therapies for RA should be registered with the BSRBR-RA. It is recognized though that recruitment may be affected by external factors in the UK such as NICE technology assessment, funding by National Health Services (NHS)/trusts, uptake by prescribing rheumatologists, and local issues at sites including resources. Patients eligible for enrolment in BSRBR-RA include RA patients with a diagnosis of RA by a consultant rheumatologist who are within 6 months of first exposure to a biologic, biosimilar, or other new advanced therapy drug, who have had a minimum of one treatment with a biologic, biosimilar, or other advanced therapy agent, are aged 16 years or older (no upper age limit), and who show willingness to give informed consent for long-term follow-up. Patients in the csDMARDs cohort are required to have active RA at recruitment (DAS28 >= 4.2) despite current treatment with at least one csDMARD.

The BSRBR-RA study is being conducted in accordance with legal and regulatory requirements, as well as with scientific purpose and will follow accepted research practices described in the guidelines for Good Pharmacoepidemiology Practices (GVP) for Post-authorisation safety studies, EMA and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guide on Methodological Standards in Pharmacoepidemiology.

### 9.2.4. DANBIO

The DANBIO database is a nationwide Danish registry for research use in rheumatologic diseases such as RA, axial spondyloarthritis, and psoriatic arthritis. It has been approved by the National Board of Health and serves as a clinical database that monitors clinical quality of treatment using selected quality indicators for patients with RA in Denmark (Hetland, 2011; Ibfelt et al., 2016).

Initially, DANBIO was a voluntary registry only including patients treated with biologic drugs; but, since 2006, it has been mandatory to also include newly referred RA patients regardless of

treatment and disease duration (Ibfelt et al., 2016). By 2015, more than 26,000 patients registered with RA had been included in DANBIO. The validity of the diagnosis is high (Ibfelt et al., 2017).

Patients are reported to the database at the time of diagnosis, referral to specialized treatment, including biological therapy at the hospital, or in a private rheumatologic clinic. At the first registration, the diagnosis, date of diagnosis, age, sex, and previous medical treatment are registered. Detailed longitudinal clinical information about representative disease course, patient-reported outcomes, joint examinations, medical treatment, and side effects of treatment (if any) are collected as part of routine care (Hetland, 2011).

DANBIO is easily linked to other data sources (including the Danish National Patient Register, the Danish Cancer Registry, or administrative registries holding socioeconomic information in Statistic Denmark) using the unique personal identification number assigned to all Danish citizens (Schmidt et al., 2015). A nationwide biobank (i.e., blood and synovial fluid) associated with DANBIO was established in 2015 (Kringelbach et al., 2018).

### 9.2.5. RABBIT

The German biologics register RABBIT is an independent academic driven prospective long-term observational cohort study of patients with RA. RABBIT is being conducted by the Deutsches Rheuma Forschungszentrum Berlin (German Rheumatism Research Centre Berlin [DFRZ]) with a joint grant of several pharmaceutical companies. The aim of the registry is to provide safety and effectiveness data on all licensed biologic and other targeted synthetic therapies provided they are available for the treatment of RA and the respective company is participating in RABBIT. The major aims of the registry are:

- To study the long-term safety of biologic agents and JAK inhibitors. This includes the observation of all AEs and serious adverse events (SAEs) in order to assess the overall safety profile. Specific emphasis will be put on the “events of interest” (refer to Section 9.3.6).
- To describe the long-term effectiveness of treatment with biologic agents and JAK inhibitors (disease outcomes on therapy as well as after terminating therapy). Major outcomes include disease activity (disease activity score-28 [DAS-28] response, clinical disease activity index [CDAI], simplified disease activity index [SDAI] or DAS-28 remission), American College of Rheumatology (ACR) 20/50/70 response, time under therapy, and functional status.
- To describe health care consumption and work disability with different drugs.

RA-treating physicians (rheumatologists) who want to participate in RABBIT must sign a contract with the DRFZ. The principal investigators, the scientific advisory board, and the pharmaceutical companies sponsoring the study have no influence on treatment decisions. The type of treatment administered and the conduct of individual therapy including dosages is solely determined by the treating physician in agreement with the patient. Patients fulfilling the following criteria can be registered in RABBIT: a diagnosis of RA (up to December 2016: per ACR 1987 criteria; or since January 2017: per diagnosis by a rheumatologist and indication of the number of ACR 1987 criteria met); age at enrolment of >=18 years; age of RA onset >15

years; initiated treatment with a licensed biologic agent or JAK inhibitor; initiated treatment with csDMARD (without concomitant biologic or targeted therapy) after failure of at least 1 csDMARD (control group); and provided a signed informed consent.

### 9.2.6. Inclusion and Exclusion Criteria

For all analyses, the index date will be the date each patient starts their respective treatment. For the filgotinib cohort, this is the date of the first administration of filgotinib. For the comparator cohorts the index date will be the first administration of the treatment that defines the cohort. This is the first administration of this treatment in the study period and represents an initiation of a new treatment line.

A patient can be present in more than one cohort and thus may have more than one index date should the patient switch between the treatment that define the cohorts (e.g., discontinues a bDMARD and initiates filgotinib).

The patient follow-up time is defined as the time from the treatment-specific index date until the earliest of treatment discontinuation, study withdrawal (withdrawn from the registry, death, or loss to follow-up) or end of study (completion of follow-up for the registry).

To be included a patient has to be aged 18 years or older at the index date. Further inclusion criteria are specified in the following sections for each registry and for each cohort; patients must meet all inclusion criteria. The cohorts are summarized in Table 3.

**Table 3 Summary of treatment cohorts by registry.**

| Cohort | ARTIS | BIOBADASER | BSRBR | DANBIO | RABBIT |
|---|---|---|---|---|---|
| Filgotinib | X | X | X | X | X |
| bDMARD | X | X[1] | X | X | X[2] |
| csDMARD (bDMARD & tsDMARD naive) | X | | X | X | X[3] |
| bDMARD (historic) | | X | | | |
| General population | X | | | X | |

[1]From 1/2016.
[2]tsDMARD naive.
[3]Failure of one prior csDMARD.

#### 9.2.6.1. ARTIS

##### *9.2.6.1.1. Inclusion Criteria*

**RA Patients Treated with Filgotinib (Filgotinib Cohort)**

1. Initiation of filgotinib treatment as captured in ARTIS
2. RA diagnosis by a consulting rheumatologist

**RA Patients Treated with bDMARDs (bDMARD Cohort)**

1. Initiation of bDMARD treatment as captured in ARTIS
2. RA diagnosis by a consulting rheumatologist that must have occurred after 1 January 2014 (to ensure a contemporaneous cohort with the filgotinib cohort)

**RA Patients Treated with csDMARD Who Are bDMARD- and tsDMARD-naive (csDMARD Cohort)**

1. Patients with at least 2 separate visits with main or secondary RA diagnosis (International Classification of Diseases [ICD] version 10 codes: M05, M06.0, M06.2, M06.3, M06.8, M06.9, M12.3) in the Swedish Patient Register, inpatient or outpatient component, one of which is from a department of Rheumatology or Internal Medicine (RA diagnosis by a consulting rheumatologist is not possible for bDMARD- and targeted synthetic disease-modifying antirheumatic drug (tsDMARD)-naive patients)
2. Patients are censored from this cohort when they start their first-ever bDMARD or tsDMARD but are eligible for subsequent inclusion into the cohorts defined above.

**General Population Cohort**

1. The collective study population in the -biologics-treated cohorts will be matched (1:5, by year of birth, sex, county of residence, and vital status at the date of first identification of arthritides) to the Swedish Total Population Register. Date of entry in the general population comparator cohorts will be set to date of entry of their corresponding RA patient.

#### *9.2.6.1.2. Exclusion Criteria*

1. Patients who do not meet the inclusion criteria will be excluded from the study.

### 9.2.6.2. BIOBADASER

#### *9.2.6.2.1. Inclusion Criteria*

***RA Patients Treated with Filgotinib (Filgotinib Cohort)***

1. RA patients enrolled in BIOBADASER
2. Initiation of filgotinib treatment as captured in BIOBADASER

***RA Patients Treated with bDMARDs (Contemporaneous bDMARD Cohort)***

1. RA patients enrolled in BIOBADASER
2. Initiation of bDMARD treatment as captured in BIOBADASER on or after January 2016

***Historic RA Patients Treated with bDMARDs (Historic bDMARD Cohort)***

1. RA patients enrolled in BIOBADASER
2. Initiation of bDMARD treatment as captured in BIOBADASER on or before December 2015

#### *9.2.6.2.2. Exclusion Criteria*

1. Patients who do not meet the inclusion criteria will be excluded from the study.

### 9.2.6.3. BSRBR-RA

#### *9.2.6.3.1. Inclusion Criteria*

***RA Patients Treated with Filgotinib (Filgotinib Cohort)***

1. RA patients enrolled in BSRBR-RA
2. Initiation of filgotinib treatment within 6 months of enrolment in BSRBR-RA

***RA Patients Treated with bDMARDs (bDMARD Cohort)***

1. RA patients enrolled in BSRBR-RA
2. Initiation of adalimumab, etanercept, or infliximab as their first bDMARD within 6 months of enrolment in BSRBR-RA

***RA Patients Treated with csDMARD Who Are bDMARD- and tsDMARD-naive (csDMARD Cohort)***

1. RA patients enrolled in BSRBR-RA between 2002 and 2008
2. RA patients treated with csDMARDs who are bDMARD- and tsDMARD- naive
3. Active RA at recruitment (defined as DAS28 >= 4.2) despite current treatment with at least one csDMARD (in order to control for confounding due to disease severity)

#### *9.2.6.3.2. Exclusion Criteria*

1. Patients who do not meet the inclusion criteria will be excluded from the study.

### 9.2.6.4. DANBIO

#### *9.2.6.4.1. Inclusion Criteria*

**RA Patients Treated with Filgotinib (Filgotinib Cohort)**

1. RA patients enrolled in DANBIO
2. Initiation of filgotinib treatment as captured in DANBIO

**RA Patients Treated With bDMARDs (bDMARD Cohort)**

1. RA patients enrolled in DANBIO with an RA diagnosis after 01-January-2014 (to ensure a contemporaneous cohort with the filgotinib cohort)
2. Initiation of bDMARD treatment as captured in DANBIO

**RA Patients Treated With csDMARD Who Are bDMARD and tsDMARD Naive (csDMARD Cohort)**

1. RA patients enrolled in DANBIO
2. RA patients treated with csDMARDs who are bDMARD and tsDMARD naive
3. Patients are censored from this cohort when they start their first ever bDMARD or tsDMARD but are eligible for subsequent inclusion into the cohorts defined above

**General Population Comparator Cohort**

The collective study population in the biologics-treated cohorts is matched (1:5, by year of birth, sex, and vital status at the date of first identification of arthritis) to the Danish Population Register. Date of entry in the general population comparator cohort is set to date of entry of their corresponding RA patient.

#### *9.2.6.4.2. Exclusion Criteria*

1. Patients who do not meet the inclusion criteria will be excluded from the study.

### 9.2.6.5. RABBIT

#### *9.2.6.5.1. Inclusion Criteria*

**RA Patients Treated with Filgotinib (Filgotinib Cohort)**

1. RA patients enrolled in RABBIT (>=18 years old, disease started after 16 years of age, fulfilling diagnosis criteria for RA)
2. Initiation of filgotinib treatment as captured in RABBIT

**RA Patients Treated with bDMARDs (bDMARD Cohort)**

1. RA patients enrolled in RABBIT after 01-January-2009
2. Initiation of bDMARD treatment as captured in RABBIT
3. No prior exposure to tsDMARDs

**RA Patients Treated with csDMARD Who Are bDMARD- and tsDMARD-naive (csDMARD Cohort)**

1. RA patients enrolled in RABBIT after 01-January-2009
2. Failure of at least 1 csDMARD and initiation of a new csDMARD as captured in RABBIT
3. No prior exposure to bDMARDs or tsDMARDs

#### *9.2.6.5.2. Exclusion Criteria*

1. Patients who do not meet the inclusion criteria will be excluded from the study.

## 9.3. Variables

Age (or date of birth), sex, disease duration, and the disease activity score-28 "DAS28" are recorded at baseline for all registries. Other variables captured at baseline and during patient follow-up are summarized for each register; the definitive set of covariates, at baseline and during follow-up, will be included in the statistical analysis plan (SAP).

### 9.3.1. ARTIS

**Patient Baseline Characteristics**

Baseline variables include:

- Rheumatoid factor [RF] positive
- Calendar year of treatment initiation
- Health Assessment Questionnaire [HAQ]
- Concomitant treatment:
  - csDMARDs, steroids, and/or nonsteroidal anti-inflammatory drugs
- Previous bDMARDs and/or tsDMARDs use
  - Number of previous treatment lines
  - Reasons for discontinuation
- Disease history:
  - malignancies
  - myocardial infarction (MI)
  - diabetes mellitus
  - others

**Patient Follow-up Data**

For each cohort and each outcome assessment, follow-up time will start with treatment start (index date) and will end at the first of the following:

- The safety event of interest
- First date of emigration from Sweden
- Date of death
- End of study period (8 years from filgotinib treatment initiation or from index date for patients in the comparator cohorts)

### 9.3.2. BIOBADASER

**Patient Baseline Characteristics**

Patients' baseline characteristics captured by BIOBADASER are collected from the recruiting clinician or directly from each patient enrolled in the registry using an electronic standardized form and include:

- Weight and height
- RA diagnosis, and date of diagnosis
- RA treatment history with other biologic, biosimilar, or targeted drugs, including the initiation and termination dates of these treatments and reasons for interruption
- All current RA therapy, including the trade name of the treatment and its active ingredient, the start and end dates, and concomitant treatments
- Comorbidities to calculate the modified Charlson Comorbidity Index (CCI)
- History of tuberculosis
- History of hyperlipidemia
- Disease activity including number of swollen joints (28), number of tender joints (28), visual analog scale (VAS), erythrocyte sedimentation rate (ESR), C-reactive protein, and RF. DAS28 is recorded if the above information is not available
- Laboratory data (where reported, most recent) including value, units and date of:
  - Absolute neutrophil count (ANC)
  - Absolute lymphocyte count (ALC)
  - Hemoglobin (Hb)
  - High-density lipoprotein (HDL) cholesterol
  - Low-density lipoprotein (LDL) cholesterol
  - Total cholesterol
  - Triglycerides

**Patient Follow-up Data**

BIOBADASER follow-up data are collected as part of patients' follow-up visits, which take place at least annually, and include:

- RA treatment switches and reasons for interruption
- Disease activity including number of swollen joints (28), number of tender joints (28), VAS, ESR, C-reactive protein (CRP), and RF. DAS28 is recorded if the above information is not available
- AEs

Operational definitions of adverse reactions and SAEs by BIOBADASER are in line with standard regulatory definitions. In addition, medical events that are not immediately life-threatening or do not cause death, but are dangerous or require intervention in order to prevent an

SAE are considered significant AEs. The following information is collected from all patients presenting a significant AE:

- Date when the AE appears
- Comorbidities for the CCI at the start of treatment
- Concomitant treatments the patient was receiving when the AE appeared
- Severity of the AE (classified as serious, nonserious, or fatal)
- Outcome of the AE (classified as unknown, recovered with no sequels, recovered with sequels, not yet recovered, death due to AE, death - the drug may have contributed, death - not related to the drug, congenital malformation at birth)
- Diagnosis of hyperlipidemia and date
- Laboratory data (where reported and closest to the follow-up visit) including value, units, and date of:
  - ANC
  - ALC
  - Hb
  - HDL cholesterol
  - LDL cholesterol
  - Total cholesterol
  - Triglycerides

### 9.3.3. BSRBR-RA

**Patient Baseline Characteristics**

Patients' baseline characteristics captured by the BSRBR-RA are collected from the recruiting clinician/nurse and include:

- RA diagnosis
- Year of recalled symptom onset
- Drug history of csDMARDs and biologic, biosimilar, or other new advanced therapy, including duration of therapy
- Significant comorbidity
- All current therapy
- Tuberculosis screening
- Coronavirus disease 2019 (COVID-19) vaccination
- HAQ and EuroQol – 5 Dimensions (EQ-5D) questionnaire
- Height, weight, and blood pressure

In addition, the BSRBR-RA captures some personal and medical information obtained directly from patients including:

- Smoking history (current, former, or never)
- Occupation and working status (full time, part time, unemployed, unable to work, or retired)
- Alcohol consumption
- Race

**Patient Follow-up Data**

The follow-up of all study participants is coordinated by the BSRBR-RA team at the University of Manchester and includes information on:

- RA treatment changes including biologic, biosimilar, and other targeted therapies received in the previous observation period
- Development of any SAEs including but not limited to the AEs of interest
- Non-serious AEs
- DAS28
- COVID-19 vaccination

### 9.3.4. DANBIO

**Patient Baseline Characteristics**

Baseline variables include:

- Rheumatoid factor (RF) positive
- Calendar year of treatment initiation
- Multi-Dimensional Health Assessment Questionnaire [MD-HAQ] (from which the HAQ can be calculated
- Concomitant treatment:
  - csDMARDs, steroids, and/or nonsteroidal anti-inflammatory drugs
- Previous bDMARDs and/or tsDMARDs use
  - Number of previous treatment lines
  - Reasons for discontinuation
- Disease history:
  - malignancies
  - MI
  - diabetes mellitus
  - others

Patients are reported to the database at the time of diagnosis, referral to specialized treatment, including biological therapy at the hospital or at a private rheumatologic clinic. At the first registration, the diagnosis, date of diagnosis, and other disease-related variables (including previous DMARD treatments, anti-cyclic citrullinated peptide, and immunoglobulin M rheumatoid factor status, disease activity measures), sociodemographic factors, and health behavioral factors (including tobacco use) are registered.

**Patient Follow-up Data**

At later visits, and at least once yearly, information regarding patients' perceived disease activity (including pain and functional status) is collected from patients via touch screens. Measures like swollen and tender joint counts, C-reactive protein, current treatment, treatment effectiveness, and adverse drug reactions (ADRs), if any, are registered by the treating physician as part of routine care.

For each cohort and each outcome assessment, follow-up time will start with treatment start (or for comparator cohorts not defined by treatment by an index date) and will end at the first of the following:

- The safety event of interest
- First date of emigration from Denmark
- Date of death
- End of study period (8 years from filgotinib treatment initiation or from index date for patients in the comparator cohorts)

### 9.3.5. RABBIT

**Patient Baseline Characteristics**

This study will make secondary use of existing data in the RABBIT registry. Data in RABBIT are reported by the recruiting physicians and the patient using a standardized form. The information captured at the first registration in RABBIT include:

- Patient sociodemographic characteristics (height, weight, and smoking [current and history])
- RA diagnosis (up to December 2016: per ACR 1987 criteria; or since January 2017: per diagnosis by a rheumatologist and indication of the number of ACR 1987 criteria met)
- Disease characteristics including treatment history, and presence of RF
- History of immunosuppressive csDMARDs, bDMARDs (original and biosimilar), or tsDMARDs, including duration of therapy recorded as start month/year, and reasons for interruption
- C-reactive protein, erythrocyte sedimentation rate, swollen joint count, tender joint count, DAS28, CDAI, and SDAI
- Patient reported functional status (Hannover Functional Status Questionnaire)
- Patient reported pain and fatigue, sleep disturbances (0 to 10 rating scales)
- Patient's assessment of general health (0 to 10 rating scale)

- Patient reported quality of life (36-Item Short Form Survey)
- Working status (full-time or part-time employment, or early retirement) (patient reported)
- Time on sick leave (patient reported)
- Comorbidities
- Vaccinations

**Patient Follow-up Data**

Follow-up data in RABBIT derive from follow-up visits at 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, and 120 months after registration and include safety (i.e, occurrence of AEs and SAEs, pregnancy and outcome, and mortality) and effectiveness outcomes (mentioned above).

All serious and nonserious AEs occurring during the observation period are regularly reported (at every follow-up visit) by the treating physician and captured in the registry. For events of special interest, detailed queries are sent out to get more information on the events (including discharge letters from hospitals, or results from biopsies, etc). According to the RABBIT protocol, AEs and SAEs are being recorded according to the International Council for Harmonisation (ICH) guidelines on clinical safety data management. Therefore, any untoward medical occurrence observed in a patient has to be reported as an AE. The AE does not necessarily have to have a causal relationship to the treatment of the patient. Any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect has to be reported as an SAE. These definitions of AEs and SAEs are also provided in the RABBIT case report forms (CRFs). For nonserious AEs, severity grading is performed according to the recommendations of the Outcome Measures in Rheumatology (OMERACT) Toxicity Working Group. For the coding of AEs and SAEs, the Medical Dictionary for Regulatory Activities (MedDRA) is used on the preferred term level. It is intended to update the AE/ SAE database with every update of MedDRA.

### 9.3.6. Endpoints of Interest

The following important identified and potential risks listed in the RMP have been prespecified:

- Serious and opportunistic infections
- Herpes zoster and primary Varicella infection
- MACE (excluding VTE)
- VTE (including DVT, PE)
- Hyperlipidemia
- Malignancies (excluding NMSC)
- NMSC
- GI perforation
- All-cause mortality

Definition of the safety endpoints of interest is provided in Annex 6. This definition list may be expanded following agreement by each registry investigators and the MAH before the comparative analysis and the final safety report. These decisions will be made prior to initiation of analyses and documented in the SAP.

### 9.3.7. Exposures of Interest

The exposures of interest are summarized by data source in Table 3.

#### 9.3.7.1. End of follow-up / person-time at risk

As detailed by each data source throughout Section 9.7, follow-up (and person-time at risk) for acute outcomes will end 90 days after discontinuing current treatment (where applicable) or when the patient will transition to another cohort or treatment, whichever occurs first (see also Section 9.3.7.2).

#### 9.3.7.2. Switching

In registries, where this is feasible, in situations of switching between different treatment cohorts (not applicable for switching drugs within the same treatment cohort), 2 approaches will be considered. For attribution of events other than malignancies or NMSC occurring within the 90-day risk window after discontinuation of cohort treatment, the event will be attributed to the new treatment cohort the patient was switched to. In a sensitivity analysis, the event will be attributed to the treatment that was discontinued (for details by registry, see Section 9.7.1 [ARTIS], Section 9.7.2 [BIOBADASER], Section 9.7.3 [BSRBR-RA], Section 9.7.4 [DANBIO], and Section 9.7.5 [RABBIT]).

For case attribution of malignancies and NMSC, see details in Section 9.7.

#### 9.3.7.3. Combination therapy

In registries, where this is feasible, users of filgotinib will additionally be stratified based on whether they initiate filgotinib as monotherapy or as combination therapy with methotrexate at their index date (= start of follow-up). Analyses of the filgotinib cohort will therefore additionally be stratified into sub-groups according to combination therapy with methotrexate (yes/ no) at index date (for more details, see also Section 9.7).

### 9.3.8. Confounding Variables

Information on covariates which may be considered in the final analysis due to their potential to confound the association between exposure to medication indicated for RA and the outcomes under the investigation can be found in Annex 7 – Table 4. The covariates may be subjects to changes over time (depending on possible new findings).

## 9.4. Data Sources

### 9.4.1. ARTIS

Safety outcomes are assessed in ARTIS through 2 mechanisms: spontaneous reports of ADRs, and linkage to the national health care registries of Sweden.

**The SRQ and ARTIS**

SRQ/ ARTIS incorporates a structured system of reporting serious and nonserious ADRs to the Swedish MPA for regular spontaneous reporting of serious ADRs using a web-based link in the SRQ.

Reports on nonserious AEs are categorized as mild or moderate. SAEs are classified according to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) standard, and categorized as (i) serious, (ii) life--threatening, or (iii) lethal. Causality is primarily assessed by the reporting physician. However, experts from the MPA Pharmacovigilance Department make the final assessment and classification of all AE reports. Reporting is in conjunction with an ADR and action taken (ie, if the drug treatment is discontinued or modified); this is reported by the physician. The specific ADR diagnoses reported are recorded according to the Swedish MPA ADR diagnosis classification, which corresponds to the MedDRA guidelines.

SRQ is also the data source of disease activity information, which is measured by CRP, ESR, HAQ, number of swollen and tender joints, and patient's global assessment of disease (on a VAS) and physician's evaluation on a Lickert-type scale. In addition, DAS28, the European League Against Rheumatism response criteria, and the American College of Rheumatology criterion of improvement (ACR 20 to 50) can be calculated.

Data entry into SRQ is provided by the patient and the rheumatologist in conjunction with visits. Visits are scheduled according to treatment guidelines and clinical practice, which means at 0, and 3/6 months after the initiation of a new antirheumatic therapy, and thereafter in relation to the level of disease activity according to an overall treat-to-target paradigm. A Swedish prescription is valid for 1 year, which contributes to patients in remission also being seen regularly. The treating physicians enter the results into the study database via a web-based interface. Optionally, it is possible to send the data to the study secretariat on a predesigned paper form. Patients can enter their data through internet ahead of the visit, at touchscreens in the waiting room, or on paper.

**Swedish Nationwide Register Linkages**

Safety is also assessed through linking SRQ/ ARTIS to nationwide Swedish healthcare registries. Compared with the ADR reports, the registry linkage has many advantages in providing data on all comorbidities that have been diagnosed, unbiased by incomplete reporting from physicians or by more or less well-founded suspicions about causality. Importantly, it also allows for obtaining data on comparator cohorts, so that any potential risk increases can be evaluated in light of risks among patients with other treatments, and the general Swedish population. The drawback is a lag

time of between 1 to 2 years from when an event occurs until it can be analyzed and reported using the registries.

**The Swedish Patient Register and the Prescribed Drug Register**

The Swedish Patient Register collects information on all hospitalized (inpatient-treated) patients, and all visits to nonprimary outpatient care (such as a visit to a rheumatologist). Diagnoses are assigned by the treating/discharging physician, as well as date of discharge, discharging hospital, and department. Diagnoses are coded according to the ICD, with Version 8 used until 1986, Version 9 from 1987 to 1996, and Version 10 since 1997. The inpatient component was originally initiated by several counties in 1964, had 85% country-wide coverage in 1983, and is considered complete since 1987. Validation against medical files have found an overall error rate in the main diagnoses of 4% at the ICD chapter-level, and 12% at the 3-digit level. The outpatient component of the Swedish Patient Register was initiated with nationwide coverage in 2001. Overall, 13% of outpatient visits lack records, but coverage is higher for somatic public care (including most rheumatology care). Chart reviews and validation of the RA diagnosis based on different algorithms applied to the registry data indicate a positive predictive value for a registry-based diagnosis of RA around 90% (Jonas K. Eriksson et al., 2013; Knight et al., 2008).

**The Swedish Cancer Register**

The Swedish Cancer Register was established in 1958 and contains information on date of cancer (and some selected pre-cancers) onset, and type of cancer according to the ICD classification and morphology/ histology. Approximately 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semiautomated, resulting in an estimated coverage greater than 95% (Barlow et al., 2009; Mattsson & Wallgren, 1984).

**The Contagious Disease Register**

The Contagious Disease Register provides events reported according the Communicable Diseases Act and the Communicable Diseases Ordinance on diseases that have mandatory reporting in Sweden. The notifiable diseases also fall into different categories: subject to mandatory contact tracing, dangerous to public health, and dangerous to society.

**The Medical Birth Register**

The Medical Birth Register contains prospectively provided data from antenatal, obstetric, and neonatal records since 1973, and covers all live and still births (but not all miscarriages) in Sweden. Among the variables covered are maternal age, parity, smoking and family situation in early pregnancy, and the infant's birth weight and length, gestational age (primarily based on ultrasound dating), and Apgar score. Complications and mother's and infant's morbidities are coded according to the ICD, with Version 8 used until 1986, Version 9 from 1987 to 1996, and Version 10 since 1997.

**The Cause of Death Register**

The Cause of Death Register is a national registry containing information on date and cause of death (underlying and contributory) for all deceased residents, including deaths among Swedish residents who died abroad. The registry was started in 1952, and the data are considered complete since 1961. From that year and onward, cause of death is missing for less than 0.5% of deceased individuals, and in 2002, a validation study estimated that only 3.3% had any errors at the 3-digit level of the ICD-coded underlying cause of death.

**The Total Population Register**

The Total Population Register was founded in 1961 and lists data on residency at a given point in time, and dates of emigration/immigration for all subjects ever residing in Sweden since 1961. This registry will be used to identify the general population comparison cohorts, and to censor subjects who die or emigrate during follow-up.

### 9.4.2. BIOBADASER

This study will be conducted by making secondary use of data collected by BIOBADASER. BIOBADASER collects baseline data from the recruiting clinician or directly from each patient enrolled in the registry using an electronic standardized form. Information is recorded by BIOBADASER (1) at baseline; (2) when an AE or change in treatment occurred (biologic therapy or with synthetic molecules with an identifiable target), for any other reason during this time period; and (3) as a part of the patient´s routine consultation used for the control of the disease or at least once a year (follow-up visit). Data are also recorded when death occurs for any reason and, in the case of discontinuation of treatment, due to remission or other causes.

Adverse events are collected in 2 ways, using an open-ended question, and using a term based on the nomenclature of the MedDRA.

### 9.4.3. BSRBR-RA

BSRBR-RA collects baseline data from the recruiting clinician/ nurse using a standardized form or directly from each patient enrolled in the registry. Follow-up data are being collected via the hospital, the patient directly, and by linkage with national databases for major health outcomes. The healthcare team at the hospital is contacted every 6 months for the first 3 years and then annually thereafter are asked to complete a standard data form covering any change in treatment over the preceding 6 or 12 months. This includes continuation on drug and dates and reasons for stopping, with details of any change in dose and commencement of any new co-therapy. Clinical information to permit calculation of the DAS28 is also collected. Additional data are also requested for all new serious comorbidities and SAEs occurring in the previous period. Event-specific questions are captured for the SAE endpoints of interest.

Registered patients are also contacted every 6 months for the first 3 years and asked to complete a patient diary that includes data about hospital admissions, new hospital referrals, and details of any new drugs prescribed. They are also asked to complete a series of questionnaires at these time points including the following:

- HAQ
- EQ-5D
- Work Productivity Survey

Following the report of any serious morbidity, either by participant or healthcare professional, the referring doctor is contacted by the BSRBR-RA and asked to provide further details, where available. For specific morbidities of interest, certain specific details are requested. All serious morbidities are coded by a trained nurse using the MedDRA system, a licensed copy of which is obtained annually.

All patients registered to BSRBR-RA are being "flagged" with the national death and cancer registries for continuous surveillance, notification of mortality, and the development of any malignancy.

### 9.4.4. DANBIO

In DANBIO, data are captured electronically from the source, requiring only little instruction of the patients and health care professionals. DANBIO has developed dedicated touch screens (and from home access) where patients enter data on, for example, disability, pain, lifestyle, and health-related quality of life, in the waiting room or from home. During the consultation, nurses, rheumatologists, and other healthcare professionals add data on, for example, joint counts and medications on their computers.

Safety outcomes are assessed in DANBIO through 2 mechanisms: spontaneous reports of ADRs from treating physicians and linkage to the national health care registries of Denmark using the unique personal identification number assigned to all Danish citizens.

The validity of the RA diagnosis in DANBIO, is >80%, and has been described elsewhere (Ibfelt et al., 2017). Registrations of medications (exposure) are prospectively validated at department level as part of the annual quality report. It is estimated, by DANBIO, that the overall error rate is <5% for the Anatomical Therapeutic Chemical level. For outcomes, these are captured through linkage with national administrative registries, which are virtually complete. The error rate varies between outcomes and is estimated to be <5% at the ICD-10 chapter-level and <10% at the three-digit level.

### 9.4.5. RABBIT

This study will be conducted by using data of the RABBIT register. Details on study design are given in Section 9.2.5. The data undergo regular internal validation checks both manually and automatically. There is no routine on-site medical chart review. However, in case of uncertainties or if insufficient data quality is suspected, there is the possibility to visit participating centers to validate and verify the reported data.

If an SAE of interest is reported, the received information is checked against hospital discharge letters or other medical files to validate the diagnosis. Where an SAE is patient reported, a

request for information is always sent to the treating rheumatologist for validation. Events that do not fall under the definition of an SAE are not subject to such additional validation.

## 9.5. Study Size

This is a descriptive study without pre-specified hypotheses. All eligible patients in each registry will be included and no upper limit on the sample size is defined. The study size target with respect to filgotinib exposure is 500 patients in each registry. However, this will depend on use of filgotinib in the respective country, which is likely to be a good measure of exposure overall in a given subpopulation and therefore provide information of public health interest.

The ability to perform comparative analyses on the incidence rates of safety endpoints between RA patients initiating filgotinib and patients in comparator cohorts will depend on statistical power and comparability between the filgotinib cohort and the comparator cohort in relation to their underlying risk of outcome development. Power calculations to detect relative risk (RR) differences between filgotinib-exposed patients and patients treated with bDMARDs are provided Annex 8 for a range of RRs, cohort sample sizes and average follow-up duration assumptions.

Assuming an average follow-up of 3 years and a risk rate of approximately 40/1000 person-years (PYs) (e.g., rate for serious infections (Askling et al., 2007; Galloway et al., 2011; Rutherford et al., 2018)), a sample size of 500 patients exposed to filgotinib and 2000 patients exposed to bDMARDs would be sufficiently powered (>80%) for detection of a 50% difference in rates between filgotinib-exposed patients and bDMARD-exposed patients. For an endpoint with a rate of 10/1000 PY (eg, malignancy (Askling et al., 2009; Mercer et al., 2015)), 500 filgotinib-exposed patients and 2000 bDMARD-exposed patients would provide enough power (> 80%) to detect a 2-fold difference between the rates observed in patients on filgotinib and patients on bDMARDs. For MACE and VTE with an estimated rate of approximately 5/1000 PY (Davies et al., 2011; Ljung et al., 2014; Low et al., 2017), a sample size of 500 filgotinib-exposed patients and 2000 bDMARD-exposed patients would be required for the detection of a 2.5-fold difference between the rates of the 2 arms with 80% power.

## 9.6. Data Management

### 9.6.1. ARTIS

This study will make secondary use of data within the ongoing ARTIS registry. The ARTIS researchers are responsible for the data management of this study.

As previously described, health and demographic information within Sweden is collected in a series of registries with a high degree of completeness resulting from the mandatory and semiautomated registration of their data. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born/immigrated thereafter, linkage of data from different registries is possible. The registries are maintained by governmental bodies (the main registries used in this study are held by the National Board of Health and Welfare [Socialstyrelsen] and Statistics Sweden [Statiskiska centralbyrån]), who may perform data linkages and provide deidentified data for research purposes.

The data warehouses of ARTIS reside on restricted, double backed-up servers at the Clinical Epidemiology Division at the Karolinska University Hospital Campus. ARTIS data are housed at the Clinical Epidemiology Division and linked to the data received from the National Board of Health and Welfare and/ or Statistics Sweden using the unique personal identification number that all Swedish residents receive. Trained staff perform this linkage, in addition to data cleaning and analysis. All work with these data warehouses is done by trained staff in adherence with local guidelines on good programming, data management practices, and archiving. Data, programs, and documents related to study reports will be maintained for a minimum of 10 years.

### 9.6.2. BIOBADASER

This study is conducted by making secondary use of data collected by BIOBADASER, who has established data management processes (Figure 3).

Data will be entered in an online application designed and will be monitored by a person specifically hired and trained to do this. In addition, these data must be downloaded to a relational database that will allow queries to be performed in order to conduct the analysis.

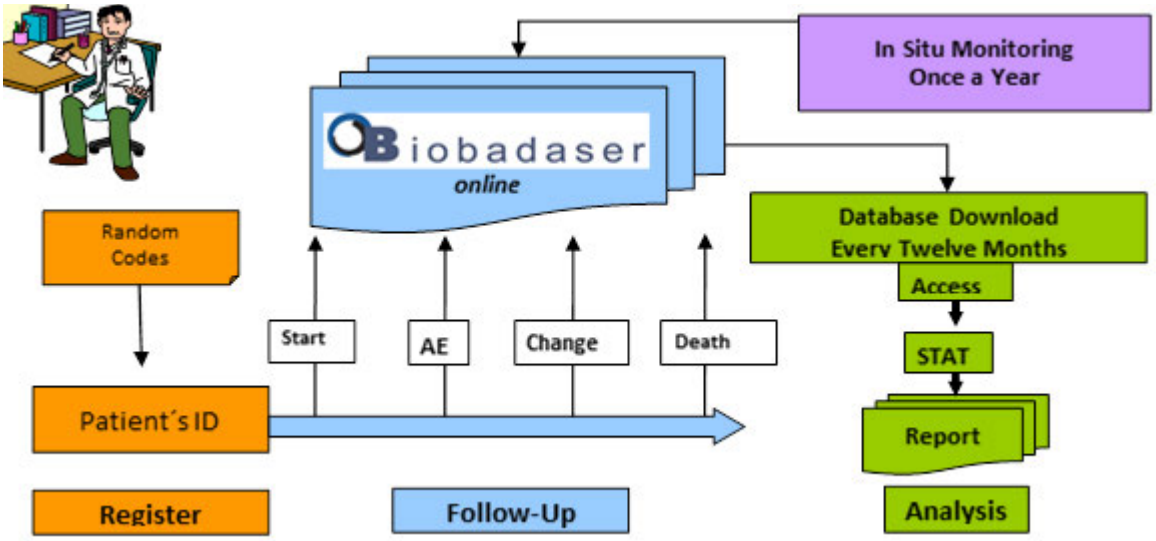



**Figure 3 Flow chart showing the data management process in BIOBADASER.**

### 9.6.3. BSRBR-RA

This study is conducted by making secondary use of data collected by BSRBR-RA, who has established data management processes.

The primary aim of the BSRBR-RA is to monitor the long-term safety of drugs used to treat rheumatoid arthritis. Clinical data is captured from NHS sites using a secure and encrypted online database. Appropriate security and governance documentation are in place including System Level Security Policy, Data Management Plan, Information Governance Risk Review, Forced Transport Layer Security for transfer of data, Stakeholder Responsibilities, and organizational standard operating procedures (SOPs) detailing data security and information governance.

SAEs, events of special interest, descriptions of events including if they led to drug discontinuation, and possible relation/ causality between AE and biologic/ biosimilar therapy (adverse drug reactions [ADRs]) are captured and reported to the pharmaceutical companies as per contractual agreements.

All SAEs are coded by a trained nurse using the industry standard MedDRA coding system.

Thus, all of the SAE notifications will be sent to the MAH and subsequently reported by the MAH to relevant health authorities in defined timelines as appropriate.

### 9.6.4. DANBIO

This study will make secondary use of data within DANBIO, which has established data management processes.

Data are collected real-time in a web-based system with user-interfaces for patients and for health professionals, which include edit checks at the time of data entry. Dataset for research purposes will go through data management before delivery.

Via a unique personal identification number that each Danish citizen receives at birth, DANBIO data can be linked to administrative registries run by the government, these are considered to be virtually complete.

### 9.6.5. RABBIT

This study is conducted by making secondary use of data collected by RABBIT, who has established data management processes.

After being enrolled (baseline visit), patients and their rheumatologists will complete questionnaires during regular follow-ups, which will take place after 3 and 6 months and afterwards every 6 months. The completed CRFs (physician and patient questionnaires) are sent by fax to the German Rheumatism Research Centre (DRFZ). To avoid misrouting, fax numbers are stored electronically in the fax machine.

Forms arriving in the central coordinating office are reviewed daily. Medical data managers are responsible for study monitoring (organization of schedules, coding, dropout research, etc.). AEs and SAEs are recorded following the ICH guidelines (CPMP/ICH/377/95/E2A). AEs and SAEs are registered continuously in a separate AE database. Diagnoses are coded using the MedDRA on the preferred term (PT) level; the coding is updated with every MedDRA update. To analyze the outcomes of interest all relevant PT terms are grouped.

Every month, a new longitudinal dataset is created by adding the new data. Twice a year a final dataset is created, which includes all answers to queries, particularly regarding SAEs and therapies. The calculations presented in the half-yearly reports are based on those datasets. Older versions of final datasets are stored electronically. The original data is kept and backups are made on a weekly basis.

## 9.7. Data Analysis

Detailed methodology for the comparative analyses of data included in this study will be documented in the SAP, which will be created by investigators from each registry, dated, filed, and archived by the MAH. The analysis for each registry will account for the availability of data and the specific composition of the comparator cohorts; the definitive set of covariates, at baseline and during follow-up, will be included in the SAP. The SAP will address several considerations that are outlined here including how patients can contribute to more than one cohort, case attribution for malignancies and use of concomitant methotrexate, how the results

will be presented (table shells) and how comparisons will be performed including the approach to modelling and adjustment for confounding from the set of covariates.

For the filgotinib cohort, concomitant use of methotrexate will be assessed at the index date (initiation). Thus, the proportion of filgotinib patients who start filgotinib while also using methotrexate will be provided. If data is available there will be a further examination of the proportion using methotrexate at a later time point (e.g., 12 months since initiation of filgotinib). In general, the timing of the onset of methotrexate and dates of discontinuation may not be specified in the registries and thus may preclude formal analysis of risks associated with methotrexate exposure.

However, where applicable, stratified analyses based on combination therapy with methotrexate at index date (yes/ no) will additionally be considered.

A person-time approach to cohort membership will be developed in the SAP for each registry. This will therefore allow for patients to contribute exposure time to more than one cohort. This can occur, for instance, when a patient who is initially in a bDMARD cohort discontinues that treatment and initiates filgotinib. The SAP will therefore detail how non-independent cohorts will be handled.

The risk function for the safety endpoints will be addressed in the SAP such that case attribution will be informed by the pharmacological/ potential toxicological impact on risk of the treatment for RA. This consideration is especially important for malignancies which may arise long after exposure to a carcinogen has terminated. Therefore, the approach will involve the attribution of observed malignancies to different scenarios of exposure such as “on drug”, “ever exposed” or “ever exposed plus an induction period”. The cases will be assigned accordingly, and the incidence rates reported.

Data analysis summarized in the protocol may be modified in the SAP to reflect usage of the most up to date methodology used by each registry.

### 9.7.1. ARTIS

All statistical analyses will be performed by ARTIS using the latest version of statistical analysis software (SAS).

**Semi-annual Reports**

The ADRs that are reported to the MPA and derived by the SRQ/ARTIS will also make up the semi-annual reports sent from ARTIS to the MAH. These reports adhere to a predefined format (Annex 3) and will contain data in the filgotinib cohort only including recruitment details, patient baseline characteristics (demographic and disease characteristics, current and previous therapies), and number and crude incidence rates of ADRs.

They will not contain data for comparator groups or patient information obtained from other registries.

**Final Safety Report**

Analyses based on registry linkages will be performed at the end of the study period (ie, 8 years after the first patient initiating filgotinib is enrolled in the registry) and at an interim time point. This interim analysis using linked data will inform the feasibility of conducting comparative analyses in the final report.

The events of interest (refer to Section 9.3.6) will be defined through linkages with the patient, and cancer and death registries, as appropriate. In addition, the Swedish national registry for contagious diseases will be used, where ARTIS gets information on tuberculosis and other possibly serious contagious diseases for which there is a mandatory registration in Sweden. ARTIS will identify endpoints of interest in the Swedish patient registry using ICD codes. Definition of endpoints of interest is provided in Annex 6.

For these analyses, the filgotinib cohort will be analyzed overall and stratified by previous biologics use. The general analytic approach will consist of comparisons with cohorts unselected and those initiating treatment with a bDMARD, stratified by previous bDMARD treatment, and a matched general population sample. In addition, covariates (status at start of follow-up) will be investigated as potential confounders. Adjusted hazard ratios will be estimated with Cox proportional hazards regression.

Regarding concomitant use of filgotinib with methotrexate at index, ARTIS does not have concrete data or a method for determining whether concomitant methotrexate is given at the time of the index date. ARTIS has previously used information on dispensed prescriptions within a certain window prior to the index date as a way of a proxy for concomitant methotrexate use. It is proposed that such an approach will be used and be added to (1) baseline descriptive tables and (2) the covariates adjusted for in comparative analyses. However, as this proxy variable will not 100% accurately capture mono-/ concomitant therapy, ARTIS will not be replicating all results stratified by these subgroups but will perform sensitivity analyses stratified by subgroups for a subset of the analyses, agreed upon prior to report delivery.

In the analyses of NMSC and malignancies incidence, subjects will be considered “ever exposed” to their respective cohort membership.

Follow-up of all other endpoints of interest (excluding NMSC and malignancies incidence) will end 90 days after discontinuing current treatment (where applicable) or when the patient will transition to another cohort or treatment, whichever occurs first. The same 90-day period will be applied for all treatment cohorts of interest accordingly.

Data will be presented as number of events, crude, and age/sex -standardized incidence rates, and when sample size permits (>=5 events in smallest strata) hazard ratios from multivariable Cox regressions.

Depending on data availability the final report will also include number of events and crude incidence rates for very elderly patients (>=75 years).

### 9.7.2. BIOBADASER

All statistical analyses will be performed by BIOBADASER using the most recent version of Stata.

**Annual Reports**

Regular descriptive reports will be provided by BIOBADASER to the MAH at 12-month intervals after enrolment is opened to filgotinib treated patients in Spain. The data collected will be summarized using descriptive statistics (counts, mean, standard deviation, median, frequencies), and in survival curves where the censoring variable will be treatment interruption or development of a safety event of interest (refer to Section 9.3.6), depending on the objective. Absolute and relative frequencies and incidence density rates (patients/year) for events of interest will also be provided.

In detail, these reports will include information for the following:

- Number of participating centers
- Number of patients under treatment who have been included as well as their description:
  - Sex
  - Age at the beginning of treatment
  - Diagnosis
  - Disease duration at the beginning of treatment
  - Biologic treatments being received

- Information on treatment interruptions:
  - Absolute and relative frequency of interruptions and reasons for discontinuation
  - Survival curve until interruption
  - Absolute and relative frequency of interruption due to ineffectiveness
  - Absolute and relative frequency of interruptions due to AEs
  - Absolute and relative frequency of interruptions due to other reasons

- Information on AEs:
  - Absolute and relative frequency of AEs:
  - In total
  - Sorted by tracts and systems
  - Specific

**Final Safety Report**

The final analysis will be conducted at the end of study period and will summarize descriptive statistics for patients initiating filgotinib (in all patients and in subgroups defined by baseline characteristics [depending on sufficient sample size]) as well as for patients in the comparator

cohorts. Number of events and crude incidence rates will be tabulated for each cohort and safety endpoint of interest. Depending on data availability, the final report will also include number of events and crude incidence rates for very elderly patients (>= 75 years).

As well as describing the rate of diagnosed hyperlipidemia, the lipid profile (HDL and LDL levels) will be described at baseline (index date). Furthermore, the lipid levels over time will be described as will the changes in lipid level with respect to baseline. Detailed description of the analysis of lipid levels will be provided in the SAP which will consider the role of missing values, use of within-patient change in lipid levels and how to compare levels and changes in lipid levels between the filgotinib cohort and the comparator cohort(s).

A draft set of MedDRA codes defining these endpoints is provided in Annex 6. A final common set of MedDRA codes and MedDRA version to define the endpoints will be provided in the SAP. The codes will be harmonized with other registries conducting similar analysis. This list may be extended following agreement by the BIOBADASER investigators and the MAH before the comparative analysis for the final safety report. These decisions will be made prior to initiation of analyses and will be documented in the SAP.

The assignment of an AE to a treatment will consider the treatment start date, the treatment end date, the half-life of each drug, the date of onset of the AE, and the time a patient would be "at risk" for an AE. The data download date from the BIOBADASER registry will be considered as the censoring date. For example, for AEs, except malignancy and NMSC, the risk window will begin with the first dose of filgotinib or bDMARD and continue for 90 days after the end of therapy (plus relevant wash-out period). This cannot be applied for csDMARDs, as BIOBADASER is focused on studying b/tsDMARDs. Dates for csDMARDs are not recorded.

For analysis of cancer risk, 'the patient once in treatment always at risk' model will be considered. Therefore, any cancer that occurred after the start of a treatment can be assigned to that treatment.

BIOBADASER will be able to stratify analyses by baseline use of methotrexate.

Depending on adequate statistical power and comparability between the filgotinib cohort and the comparator cohorts in relation to their underlying risk of outcome development, comparative analysis between patients exposed to filgotinib and patients in the comparator cohort adjusted for potential confounders will be performed in the final analysis. Detailed information on the analyses will be provided in the SAP.

### 9.7.3. BSRBR-RA

All statistical analyses will be performed by BSRBR-RA using the most recent version of Stata.

**Semi-annual Reports**

Regular reports adhering to a predefined format, "the Manchester Template" (Annex 4), will be provided by BSRBR-RA to the MAH at 6-month intervals after enrolment is opened to filgotinib treated patients in the UK. These reports will include recruitment details, baseline characteristics

(demographic and disease characteristics, current and previous therapies), and crude incidence rates for a range of prespecified events (refer to Section 9.3.6).

**Final Safety Report**

The final analysis will be conducted at the end of study period and will summarize descriptive statistics for patients initiating filgotinib (in all patients and in subgroups defined by baseline characteristics [depending on sufficient sample size]) as well as for patients in the comparator cohorts. Number of events and crude incidence rates will be tabulated for each cohort and safety endpoint of interest (refer to Section 9.3.6). Depending on data availability, the final report will also include number of events and crude incidence rates for very elderly patients (>= 75 years).

A draft set of MedDRA codes defining these endpoints is provided in Annex 6. A final common set of MedDRA codes and MedDRA version to define the endpoints will be provided in the SAP. The codes will be harmonized with other registries conducting similar analysis. Hyperlipidemia cannot be operationalized using BSRBR-RA data. This list may be extended following agreement by BSRBR-RA investigators and the MAH before the comparative analysis for the final safety report. These decisions will be made prior to initiation of analyses and will be documented in the SAP.

For all AEs except malignancy and NMSC, the risk window will begin with the first dose of filgotinib or bDMARD (i.e., adalimumab, etanercept, or infliximab) and continue for 90 days after the end of therapy, date of last received follow-up form, and death or the cut-off date for this report, whichever comes first. SAEs that occur outside of this risk window will not count for purposes of incidence rate estimation. For patients in the csDMARD cohort, follow-up time will start at entry to study and continue until death, the date of last received follow-up form, or until the patient starts a biologic drug. The report can only include patients for whom at least 1 follow-up form has been returned.

For analyses of risk of malignancy, the analysis will assume an ‘ever exposed’ model of risk assessment and therefore, the risk window for patients in the filgotinib cohort and the bDMARD cohort (ie, patients treated with adalimumab, etanercept, or infliximab) will include all person-time in the registry from the start of therapy and extend until death or the cut-off date for this report, whichever comes first, even in case of subsequent switching to another biologic agent. For patients in the csDMARD cohort, follow-up time will start at entry to study and continue until death, the cut-off date, or until the patient starts a biologic drug.

For analyses of risk of death, both risk windows will be used − an ‘on-drug’ model and an ‘ever exposed’ model. For the ‘ever-exposed’ model, see risk of malignancy above. For the ‘on-drug’ model, as reports of death come to the registry independent of follow-up forms, the risk window will begin at the start of therapy with filgotinib for patients in the filgotinib cohort or at the start of therapy with adalimumab, etanercept, or infliximab for patients in the bDMARD cohort, and continue for 90 days following end of therapy, death, or the cut-off date for this report, whichever comes first, even in cases of subsequent switching to any of the remaining biologic or targeted synthetic agents during the 90 days following end of therapy. Results of both models will be presented.

Depending on adequate statistical power and comparability between the filgotinib cohort and the comparator cohorts in relation to their underlying risk of outcome development, comparative analysis between patients exposed to filgotinib and patients in the comparator cohort adjusted for potential confounders will be performed in the final analysis. The key confounders to be measured at baseline include details of disease severity, including symptom duration, current HAQ, current significant comorbidities, and all relevant previous therapies. In order to control for confounding due to the disease status, patients of the historic csDMARDs cohort will be required to have baseline DAS28 >= 4.2 despite current treatment with at least 1 csDMARD.

Since the latest targeted therapies include a new generation of bDMARDs and tsDMARDs, patients who are prescribed these drugs may include patients who probably failed adalimumab, etanercept, infliximab, or csDMARDs, and thus are more likely to be those who had more severe disease, longer disease duration, and more comorbidities than the comparison groups. Therefore, the BSRBR-RA also has the option to select subsets of patients from within exposed cohorts who can form a more appropriate comparison cohort for analysis.

It is very important to control for the related confounding during analyses in addition to the inclusion criteria. For this reason, after applying all the inclusion criteria, statistical adjustment, especially using propensity scoring techniques, will be adopted to control for the potential residual confounding. Stratified analysis or subgroup analysis will also be considered for major confounding factors if deemed appropriate after descriptive analysis. Furthermore, sensitivity analysis will be conducted to evaluate the impact of disease severity, duration, and medical treatment history on the results for any residual confounding that may remain after application of inclusion/exclusion and statistical adjustment in the modelling, and to better understand the impact of analytical decisions on the results.

### 9.7.4. DANBIO

All statistical analyses will be performed by DANBIO. Analyses will be performed using the latest version of R or SAS.

**Semi-annual Reports**

The reported ADRs by the treating physicians will also make up the semi-annual reports sent from DANBIO to the MAH. These reports will contain data in the filgotinib cohort only, including recruitment details, baseline characteristics (demographic and disease characteristics, current and previous therapies), and number and crude incidence rates of ADRs. They will not contain data for comparator groups or patient information obtained from other registries (linkage).

**Final Safety Report**

Analyses based on registry linkages will be performed at the end of the study period (ie, 8 years after the first patient initiating filgotinib is enrolled in the registry) and at an interim time point. The feasibility of conducting comparative analyses on the incidence rates of safety endpoints between RA patients initiating treatment with filgotinib and patients on comparator cohort will

depend on statistical power and comparability between the filgotinib cohort and the comparator cohort in relation to their underlying risk of outcome development.

The endpoints of interest (refer to Section 9.3.6) will be defined through linkages with the patient, cancer, and death registries, as appropriate. Definition of events of interest is provided in Annex 6.

Adjusted hazard ratios will be estimated with Cox proportional hazards regressions adjusted for potential confounders. Data will be presented as number of events, crude and standardized incidence rates, and, if sample size permits, hazard ratios from multivariable Cox regressions.

In the analyses of NMSC and malignancies incidence, subjects will be considered "ever exposed" to their respective cohort membership. Follow-up of all other events of interest (excluding NMSC and malignancies incidence) will end 90 days after discontinuing current treatment (where applicable), death or when the patient will transition to another cohort or treatment, whichever occurs first.

Depending on data availability, the final report will also include number of events and crude incidence rates for the very elderly patients (>=75 years).

### 9.7.5. RABBIT

All statistical analyses will be performed by RABBIT using the most recent version of SAS.

**Semi-annual Reports**

Regular reports adhering to a predefined format, "the Manchester Template" (Annex 5), will be provided by RABBIT to the MAH at 6-month intervals after enrolment is opened to filgotinib-treated patients in Germany. These reports will include recruitment details, baseline characteristics (demographic and disease characteristics, current and previous therapies), and crude incidence rates for a range of prespecified events (refer to Section 9.3.6). The MAH will receive 3 reports, 1 for patients in the filgotinib cohort and 2 reports for the patients in the 2 comparator cohorts (control group: includes all patients who registered in RABBIT with the start of a csDMARD therapy; mixed control group: includes all patients who start a csDMARD therapy during follow-up after ending a bDMARD or tsDMARD therapy).
Copies of all summary reports will be sent by RABBIT to the members of the scientific advisory board and the spokesman of the commission drug therapy of the German Society for Rheumatology (DGRh).

**Final Safety Report**

The final analysis will be conducted at the end of study period and will summarize descriptive statistics for patients initiating filgotinib (in all patients and in subgroups defined by baseline characteristics [depending on sufficient sample size]) as well as for patients in the comparator cohorts. Number of events and crude incidence rates will be tabulated for each cohort and safety endpoint of interest (refer to Section 9.3.6). Depending on data availability, the final report will also include number of events and crude incidence rates for very elderly patients (>=75 years).

A draft set of MedDRA codes defining these endpoints is provided in Annex 6. A final common set of MedDRA codes and MedDRA version to define the endpoints will be provided in the SAP. The codes will be harmonized with other registries conducting similar analysis. This list may be extended following agreement by RABBIT investigators and the MAH before the comparative analysis for the final safety report. These decisions will be made prior to initiation of analyses and will be documented in the SAP.

A 3-month risk window is used to assign events to treatments. The 3-month risk window approach is applied for the analyses of all outcomes except pregnancy-related adverse outcomes.

Starting with the first month after discontinuation of a bDMARD, 3 months of therapy are added to the exposure time (in case of rituximab: 9 months). This implies that a patient may contribute person- time of exposure to several bDMARDs at the same time if treatments were switched without lag time.

tsDMARDs (including filgotinib) are treated like bDMARDs regarding assignment of SAEs and a 3-month risk window is applied as for bDMARDs.

For patients enrolled with csDMARD no risk window is applied after bDMARD initiation. Thus, patients contribute observation time to the respective bDMARD group without applying a risk window for the csDMARD exposure, and events are assigned to the bDMARD solely, if they occur after bDMARD start.

If a patient starts another treatment and an SAE of interest occurs within 3 months after stopping the prior treatment,the SAE is assigned to the prior AND the actual treatment. This is different for csDMARDs, for which the follow-up will end after starting ts- or bDMARDs.

For malignancies, additionally to the “on drug”- approach with 3 months risk window, a patient is considered as once exposed to a substance then ever at risk (with orwithout adding a 180-day induction period to the treatment start).

Filgotinib users will be described at least descriptively according to their prescription at mono- or combi therapy. RABBIT does not know yet, if it will be feasible to stratify them in more complex analyses.

Depending on adequate statistical power and comparability between the filgotinib cohort and the comparator cohorts in relation to their underlying risk of outcome development, comparative analysis between patients exposed to filgotinib and patients in the comparator cohort adjusted for potential confounders will be performed in the final analysis. Covariates to be used to assess the role of confounding will be selected from the final set of covariates which will be defined in the SAP and which are outlined in Section 9.3.5.

## 9.8. Quality Control

### 9.8.1. ARTIS

This study will make secondary use of data existing within the ARTIS registry. ARTIS works mainly with data from the SRQ, a “quality-of-care” registry with several guidelines in place to

monitor and maintain data quality. Physicians working with the SRQ have access to an online portal in which they can monitor all their patients and their information. Regional representatives encourage/ remind the physicians to check the quality of the information by accessing the "Data Quality" section of the "Visit monitoring" tool. In this section a series of questions guide the doctor in checking the quality of the registered information of their patients. Moreover, the data coordinator of SRQ periodically checks the quality of the data overall in the region.

Quality control of specific reports is made in accordance with ARTIS SOPs through internal review by at least 2 members of staff: a statistician/epidemiologist responsible for assessing technical aspects and integrity of the results, and a clinical expert responsible for assessing the plausibility and consistency of observed rates and risks in relation to what is previously known on the topic. Any results that are marked as questionable or inconsistent are reanalyzed/ verified or rephrased until no more issues are identified.

### 9.8.2. BIOBADASER

This study will be conducted by making secondary use of data collected by BIOBADASER, who is responsible for data quality control.

As part of the established BIOBADASER quality control practices, the following processes will be performed to validate the collected data:

- Online monitoring on a weekly basis, performed by personnel with experience in pharmacovigilance, to detect any abnormalities in entered data and discuss these abnormalities with the clinicians who entered the data. Every 4 months, there will be a downloading of data to perform a control of quality, and a report on detected incidences and suggestions to improve data entry will be sent to researchers.
- In situ monitoring: The clinical research associate will visit each center to verify that collected data match the patient´s medical history on an annual basis. This monitoring will be performed, starting from the second year, for those centers that remain in BIOBADASER.
- The application contains filters that limit unreliable data entry (data outside permissible range, etc.).

### 9.8.3. BSRBR-RA

This study will be conducted by making secondary use of data collected by BSRBR-RA, who is responsible for data quality control. As part of the established BSRBR-RA quality control practices, all information received on SAEs is being reviewed by 1 of 2 trained registered nurses prior to coding. Reports can arise from the hospital team, patients, or the national registries. For SAEs to be included in analysis, the following information is required:

- A legible and recognized disorder/ signs and symptoms
- Date of the event
- Drug the patient was on at the time of the event

Where this information is missing, the BSRBR-RA pharmacovigilance team contacts the hospital to validate and confirm the details around the SAE. Where an SAE is patient reported, a request

for information is always sent to the hospital for validation. Events that do not fall under the definition of an SAE are not subject to such additional validation. The data undergo regular validation checks both manually and automatically.

### 9.8.4. DANBIO

This study is conducted by making secondary use of data collected by DANBIO, which is responsible for data quality control.

Data are entered by the patient and by the physician/nurse in the outpatient clinic. Data entry is part of an ongoing nationwide quality-assurance project. At time of data entry, edit checks are performed. Data are cleaned locally, and nationwide data is exported annually for the annual quality report. Coverage is assessed annually.

### 9.8.5. RABBIT

This study will be conducted by making secondary use of data collected by RABBIT, who is responsible for data quality control.

The medical data managers continuously monitor the receipts of completed forms and issue queries regarding obvious issues (missing values, faults, range violation, etc.) immediately. A check for longitudinal data plausibility is performed once a month after the longitudinal dataset was created. Special procedures are in place to call the physicians for follow-up visits and for an intensive drop out inquiry, if more than 2 follow-up time points are missing in one patient.

Every 4 weeks, reminders (and lists with patient numbers) are sent to rheumatologists to call the respective patients on the lists for follow-up visits in the next month. After 2 missed follow-up visits, the physician's office or the patient himself or herself are contacted. If a patient has switched doctors, the patient's new physician will be asked (with the patient's consent) to complete the remaining forms and to continue to follow-up of this patient. If a study patient dies, the physician is asked to report the date and cause of death to the study coordinating office. If this information cannot be provided by the rheumatologist, the team at the DRFZ will ascertain date and cause of death from the authorities.

In case of an SAE of interest or in case of an SAE that had been assigned to be possibly related to a DMARD, the treating physician is asked to complete a query form for additional information. For all SAEs of interest as well as for pregnancy and its outcomes, event-specific SAE forms are used. For SAEs that are no events of interest, but with a physician reported possible relation to DMARD use, a general additional request query is used without event-specific questions. All SAE queries comprise details for greater specification of the event, related diagnostic and therapeutic procedures, as well as details on the course of DMARD therapy. In addition, all other medications the patient had been treated with at the time of the event are reported. Also, physicians are asked to send discharge letters if available. A team of 6 people, including a physician and 4 nurses, is responsible for all processes and procedures dealing with AEs. Once a week, difficult cases are discussed with the responsible study physician/ principal investigator.

## 9.9. Limitations of the Research Methods

This non-interventional PASS aims to evaluate the long-term safety of filgotinib in the treatment of patients with moderate to severe active RA using data already collected by the well--established European registries including ARTIS, BIOBADASER, BSRBR-RA, DANBIO and RABBIT. Despite the strengths of this observational study, data must be evaluated considering their limitations. For example, consistent with most observational studies, the possibility of channeling biases, endpoint misclassification, and generalizability are of concern when evaluating event rates.

Event misclassification is of concern within the observational setting due to less stringent monitoring relative to clinical trials. While each registry has an established system to identify and capture endpoint data, it is not feasible in such an observational study to verify all events via source documentation.

This study will follow patients for a period of 8 years after study initiation. Conclusions may not be generalizable outside of the 8-year period since treatment initiation.

## 9.10. Other Aspects

### 9.10.1. Sponsor's and Investigator's Responsibilities

#### 9.10.1.1. Study Discontinuation

The MAH reserves the right to fully terminate this PASS at any time ("Full Termination"), while each registry (i.e., ARTIS, BIOBADASER, BSRBR-RA, DANBIO or RABBIT) may terminate its own participation in this PASS according to the contractual terms and conditions applicable to each collaboration ("Partial Termination"). Should either a Full Termination or a Partial Termination be necessary, the relevant parties (i.e., the MAH and each registry) will collaborate to arrange discontinuation procedures and notify the appropriate regulatory agencies, where applicable. For studies conducted for a commitment to a regulatory authority, any consideration for termination of the study will be discussed with the applicable authority beforehand.

# 10. PROTECTION OF HUMAN SUBJECTS

This study involves data that exist in an anonymized structured format and contain no patient personal information. Data protection principles from the participating registries are followed.

## 10.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The study will be conducted in accordance with the EU Guideline on Good Pharmacovigilance Practices (GVP) Module VIII – Post-Authorisation Safety Studies, including archiving of essential documents.

## 10.2. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Review

### 10.2.1. ARTIS

This study will make secondary use of existing data collected by ARTIS that are fully anonymized and contain no patient personal information. As individual subjects cannot be identified, no IRB/IEC review will be obtained by the MAH.

The ARTIS registry linkage database does not contain any patient identifying information (for example, name), except for a unique number assigned for the purpose of linking files. This comparative safety study has been approved by the Ethics Committee in Stockholm; renewed approval will be sought as needed for the duration of the study.

### 10.2.2. BIOBADASER

This study will make secondary use of existing data collected by BIOBADASER that are fully anonymized and contain no patient personal information. As individual subjects cannot be identified, no IRB/IEC review will be obtained by the MAH.

### 10.2.3. BSRBR-RA

This study will make secondary use of existing data collected by BSRBR-RA that are fully anonymized and contain no patient personal information. As individual subjects cannot be identified, no IRB/IEC review will be obtained by the MAH.

As BSRBR-RA is an observational cohort study, IRB approval is not required. Instead, the study has been approved by the NHS Multi-Research Ethics Committee in the UK (ref: MREC 00/8/53). All ethical approvals and amendments can be found under Site File Documents. In addition, the BSRBR-RA has an independent Steering Committee and Data Monitoring and Ethics Committee.

### 10.2.4. DANBIO

The data provided to the MAH from DANBIO registry will be fully anonymized. As individual subjects cannot be identified, no IRB/IEC review will be obtained by the MAH.

### 10.2.5. RABBIT

This study will make secondary use of existing data collected by RABBIT. Patient data in RABBIT are pseudo-anonymized. RABBIT will only share fully anonymized data with the MAH containing no patient information with which patients could be identified. As individual subjects cannot be identified, no IRB/IEC review will be obtained by the MAH.

## 10.3. Informed Consent

### 10.3.1. ARTIS

In accordance with Swedish law, non-interventional studies of registry-based data (including "quality-of-care" registries such as SRQ/ARTIS) do not usually require informed consent by the individual study subjects. Instead, regional ethics committees are mandated to provide permission for such studies, after weighing the subjects' potential benefit from the research against the potential risks to the subjects' personal privacy. ARTIS has ethical approval for the studies described in this protocol but is subject to strict rules and regulations regarding the maintenance, analysis and reporting of personal data.

### 10.3.2. BIOBADASER

The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. A participating researcher (a rheumatologist) is in charge of this task. After ensuring that the potential subject has understood the information, the rheumatologist must then seek the potential subject's freely given informed consent in writing. Informed consent is an inclusion criterion. Only patients who sign the informed consent can be included in the registry.

### 10.3.3. BSRBR-RA

All parties will ensure protection of patient personal data and will not include patient names or other directly identifiable data on any forms, reports, publications or in any other disclosures, except where required for regulatory purposes and in accordance with the current data protection law. In case of data transfer, the MAH will maintain high standards of confidentiality and protection of personal data.

All participants in the BSRBR-RA have provided informed consent for participation in the study (Research Ethics Committee reference: 00/8/053).

### 10.3.4. DANBIO

According to Danish law, informed consent is not required for this kind of data.

The data provided to the MAH from DANBIO will be fully anonymized and contain no patient personal information.

### 10.3.5. RABBIT

Every patient provides written informed consent before study entry. The patient consent forms meet the requirements of the Directive 95/46/EC of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

## 10.4. Confidentiality

The investigators from each registry must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only a unique identifier (as allowed by local law) and a unique study identification code should be recorded on any study-related document.

The investigators from each registry agree that all information received from the MAH, including but not limited to this protocol, and any other information of this study, remain the sole and exclusive property of the MAH during the conduct of this study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of this study or as required by law) without prior written consent from the MAH. The investigators from each registry further agree to take all reasonable precautions to prevent the disclosure by any employee or agent to any third party or otherwise into the public domain.

# 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

This is a non-interventional PASS making secondary use of existing data within the ARTIS, BIOBADASER, BSRBR-RA, DANBIO, and RABBIT registries, where individual patient data are de-identified within safety data. Therefore, the MAH will not collect or report individual case safety reports in an expedited fashion. All the safety data are collected per the registries. Individual AEs will not be solicited in this study. Safety data from this study will be presented in aggregate in the interim and final study report and in the periodic benefit-risk evaluation reports/periodic safety update reports. The interim and final study report will be considered for signal detection activities.

# 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

## 12.1. Study Report and Publications

Semi-annual summary reports adhering to a predefined format will be generated by ARTIS, BSRBR-RA, DANBIO, and RABBIT and shared with the MAH; annual summary reports will be generated by BIOBADASER and shared with the MAH.

Every 2 years, interim reports summarizing the study status will be compiled by the MAH based on information provided by the regular summary reports from the registers and submitted to the EMA and to the MHRA by the MAH every 2 years. The final safety report will be provided to the EMA and to the MHRA and will be included in RMP updates.

Study reports may be used in regulatory communications in other countries for contextualization purposes. Scientific manuscripts based on specific safety events may be developed by each registry for external publication purposes.

# 13. REFERENCES

Alamanos, Y., Voulgari, P. V., & Drosos, A. A. (2006). Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin. Arthritis Rheum.*, *36*(3), 182–188. https://doi.org/10.1016/j.semarthrit.2006.08.006

Askling, J., Fored, C. M., Brandt, L., Baecklund, E., Bertilsson, L., Feltelius, N., Cöster, L., Geborek, P., Jacobsson, L. T., Lindblad, S., Lysholm, J., Rantapää-Dahlqvist, S., Saxne, T., van Vollenhoven, R. F., & Klareskog, L. (2007). Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. *Ann. Rheum. Dis.*, *66*(10), 1339–1344. https://doi.org/10.1136/ard.2006.062760

Askling, J., van Vollenhoven, R. F., Granath, F., Raaschou, P., Fored, C. M., Baecklund, E., Dackhammar, C., Feltelius, N., Cöster, L., Geborek, P., Jacobsson, L. T., Lindblad, S., Rantapää-Dahlqvist, S., Saxne, T., & Klareskog, L. (2009). Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? *Arthritis Rheum.*, *60*(11), 3180–3189. https://doi.org/10.1002/art.24941

Barlow, L., Westergren, K., Holmberg, L., & Talbäck, M. (2009). The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol. Stockh. Swed.*, *48*(1), 27–33. https://doi.org/10.1080/02841860802247664

Carmona, L., Gómez-Reino, J., González-González, R., & en representación del Grupo de Estudio BIOBADASER. (2005). [Spanish registry of adverse events of biological therapies in rheumatic diseases (BIOBADASER): report as of january 14, 2005]. *Reumatol. Clin.*, *1*(2), 95–111. https://doi.org/10.1016/S1699-258X(05)72722-4

Carmona, Loreto, Gómez-Reino, J. J., Rodríguez-Valverde, V., Montero, D., Pascual-Gómez, E., Mola, E. M., Carreño, L., Figueroa, M., & BIOBADASER Group. (2005). Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum.*, *52*(6), 1766–1772. https://doi.org/10.1002/art.21043

Chung, W.-S., Peng, C.-L., Lin, C.-L., Chang, Y.-J., Chen, Y.-F., Chiang, J. Y., Sung, F.-C., & Kao, C.-H. (2014). Rheumatoid arthritis increases the risk of deep vein thrombosis and pulmonary thromboembolism: a nationwide cohort study. *Ann. Rheum. Dis.*, *73*(10), 1774–1780. https://doi.org/10.1136/annrheumdis-2013-203380

Combe, B., Kivitz, A., Tanaka, Y., van der Heijde, D., Simon, J. A., Baraf, H. S. B., Kumar, U., Matzkies, F., Bartok, B., Ye, L., Guo, Y., Tasset, C., Sundy, J. S., Jahreis, A., Genovese, M. C., Mozaffarian, N., Landewé, R. B. M., Bae, S.-C., Keystone, E. C., & Nash, P. (2021). Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. *Ann. Rheum. Dis.*, *80*(7), 848–858. https://doi.org/10.1136/annrheumdis-2020-219214

Cross, M., Smith, E., Hoy, D., Carmona, L., Wolfe, F., Vos, T., Williams, B., Gabriel, S., Lassere, M., Johns, N., Buchbinder, R., Woolf, A., & March, L. (2014). The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann. Rheum. Dis.*, *73*(7), 1316–1322. https://doi.org/10.1136/annrheumdis-2013-204627

Davies, R., Galloway, J. B., Watson, K. D., Lunt, M., Symmons, D. P. M., Hyrich, K. L., & BSRBR Control Centre Consortium, British Society for Rheumatology Biologics Register. (2011). Venous thrombotic events are not increased in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. *Ann. Rheum. Dis.*, *70*(10), 1831–1834. https://doi.org/10.1136/ard.2011.153536

Eriksson, J. K., Askling, J., & Arkema, E. V. (2014). The Swedish Rheumatology Quality Register: optimisation of rheumatic disease assessments using register-enriched data. *Clin. Exp. Rheumatol.*, *32*(5 Suppl 85), S-147-149.

Eriksson, Jonas K., Neovius, M., Ernestam, S., Lindblad, S., Simard, J. F., & Askling, J. (2013). Incidence of rheumatoid arthritis in Sweden: a nationwide population-based assessment of incidence, its determinants, and treatment penetration. *Arthritis Care Res.*, *65*(6), 870–878. https://doi.org/10.1002/acr.21900

Firestein, G. S., & McInnes, I. B. (2017). Immunopathogenesis of Rheumatoid Arthritis. *Immunity*, *46*(2), 183–196. https://doi.org/10.1016/j.immuni.2017.02.006

Galloway, J. B., Hyrich, K. L., Mercer, L. K., Dixon, W. G., Fu, B., Ustianowski, A. P., Watson, K. D., Lunt, M., Symmons, D. P. M., BSRBR Control Centre Consortium, & British Society for Rheumatology Biologics Register. (2011). Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatol. Oxf. Engl.*, *50*(1), 124–131. https://doi.org/10.1093/rheumatology/keq242

Genovese, M. C., Kalunian, K., Gottenberg, J.-E., Mozaffarian, N., Bartok, B., Matzkies, F., Gao, J., Guo, Y., Tasset, C., Sundy, J. S., de Vlam, K., Walker, D., & Takeuchi, T. (2019). Effect of Filgotinib vs Placebo on Clinical Response in Patients With Moderate to Severe Rheumatoid Arthritis Refractory to Disease-Modifying Antirheumatic Drug Therapy: The FINCH 2 Randomized Clinical Trial. *JAMA*, *322*(4), 315–325. https://doi.org/10.1001/jama.2019.9055

Gómez-Reino, J. J., Carmona, L., Angel Descalzo, M., & Biobadaser Group. (2007). Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum.*, *57*(5), 756–761. https://doi.org/10.1002/art.22768

Gómez-Reino, J. J., Carmona, L., Valverde, V. R., Mola, E. M., Montero, M. D., & BIOBADASER Group. (2003). Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum.*, *48*(8), 2122–2127. https://doi.org/10.1002/art.11137

Hetland, M. L. (2011). DANBIO--powerful research database and electronic patient record. *Rheumatol. Oxf. Engl.*, *50*(1), 69–77. https://doi.org/10.1093/rheumatology/keq309

Holmqvist, M. E., Neovius, M., Eriksson, J., Mantel, Ä., Wållberg-Jonsson, S., Jacobsson, L. T. H., & Askling, J. (2012). Risk of venous thromboembolism in patients with rheumatoid arthritis and association with disease duration and hospitalization. *JAMA*, *308*(13), 1350–1356. https://doi.org/10.1001/2012.jama.11741

Ibfelt, E. H., Jensen, D. V., & Hetland, M. L. (2016). The Danish nationwide clinical register for patients with rheumatoid arthritis: DANBIO. *Clin. Epidemiol.*, *8*, 737–742. https://doi.org/10.2147/CLEP.S99490

Ibfelt, E. H., Sørensen, J., Jensen, D. V., Dreyer, L., Schiøttz-Christensen, B., Thygesen, P. H., Colic, A., Raun, J. L., Manilo, N., Rødgaard, A., Poulsen, U. E., Rasmussen, C., Hansen, T., Unger, B., Pelck, R., Kincses, A., Nordin, H., Lorenzen, T., Theibich, A., Jensen Hansen, I. M., Espesen, J., Grydehøj, J., Holland-Fischer, M., Loft, A. G., & Hetland, M. L. (2017). Validity and completeness of rheumatoid arthritis diagnoses in the nationwide DANBIO clinical register and the Danish National Patient Registry. *Clin. Epidemiol.*, *9*, 627–632. https://doi.org/10.2147/CLEP.S141438

Knight, A., Sandin, S., & Askling, J. (2008). Risks and relative risks of Wegener's granulomatosis among close relatives of patients with the disease. *Arthritis Rheum.*, *58*(1), 302–307. https://doi.org/10.1002/art.23157

Kringelbach, T. M., Glintborg, B., Hogdall, E. V., Johansen, J. S., Hetland, M. L., & Biomarker Protocol Study Group. (2018). Identification of new biomarkers to promote personalised treatment of patients with inflammatory rheumatic disease: protocol for an open cohort study. *BMJ Open*, *8*(2), e019325. https://doi.org/10.1136/bmjopen-2017-019325

Lindhardsen, J., Ahlehoff, O., Gislason, G. H., Madsen, O. R., Olesen, J. B., Svendsen, J. H., Torp-Pedersen, C., & Hansen, P. R. (2012). Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ*, *344*, e1257. https://doi.org/10.1136/bmj.e1257

Listing, J., Kekow, J., Manger, B., Burmester, G.-R., Pattloch, D., Zink, A., & Strangfeld, A. (2015). Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. *Ann. Rheum. Dis.*, *74*(2), 415–421. https://doi.org/10.1136/annrheumdis-2013-204021

Ljung, L., Askling, J., Rantapää-Dahlqvist, S., Jacobsson, L., & ARTIS Study Group. (2014). The risk of acute coronary syndrome in rheumatoid arthritis in relation to tumour necrosis factor inhibitors and the risk in the general population: a national cohort study. *Arthritis Res. Ther.*, *16*(3), R127. https://doi.org/10.1186/ar4584

Low, A. S. L., Symmons, D. P. M., Lunt, M., Mercer, L. K., Gale, C. P., Watson, K. D., Dixon, W. G., Hyrich, K. L., & British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) and the BSRBR Control Centre Consortium. (2017). Relationship between exposure to tumour necrosis factor inhibitor therapy and incidence and severity of myocardial infarction in patients with rheumatoid arthritis. *Ann. Rheum. Dis.*, *76*(4), 654–660. https://doi.org/10.1136/annrheumdis-2016-209784

Ludvigsson, J. F., Otterblad-Olausson, P., Pettersson, B. U., & Ekbom, A. (2009). The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur. J. Epidemiol.*, *24*(11), 659–667. https://doi.org/10.1007/s10654-009-9350-y

Mattsson, B., & Wallgren, A. (1984). Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol. Oncol.*, *23*(5), 305–313. https://doi.org/10.3109/02841868409136026

Meissner, Y., Richter, A., Manger, B., Tony, H. P., Wilden, E., Listing, J., Zink, A., & Strangfeld, A. (2017). Serious adverse events and the risk of stroke in patients with rheumatoid

arthritis: results from the German RABBIT cohort. *Ann. Rheum. Dis.*, *76*(9), 1583–1590. https://doi.org/10.1136/annrheumdis-2017-211209

Mercer, L. K., Lunt, M., Low, A. L. S., Dixon, W. G., Watson, K. D., Symmons, D. P. M., Hyrich, K. L., & BSRBR Control Centre Consortium. (2015). Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann. Rheum. Dis.*, *74*(6), 1087–1093. https://doi.org/10.1136/annrheumdis-2013-204851

Neovius, M., Simard, J., Sundström, A., Jacobsson, L., Geborek, P., Saxne, T., Feltelius, N., Klareskog, L., Askling, J., & ARTIS Study Group. (2011). Generalisability of clinical registers used for drug safety and comparative effectiveness research: coverage of the Swedish Biologics Register. *Ann. Rheum. Dis.*, *70*(3), 516–519. https://doi.org/10.1136/ard.2010.130914

Neovius, Martin, Simard, J. F., Askling, J., & ARTIS study group. (2011). Nationwide prevalence of rheumatoid arthritis and penetration of disease-modifying drugs in Sweden. *Ann. Rheum. Dis.*, *70*(4), 624–629. https://doi.org/10.1136/ard.2010.133371

Rutherford, A. I., Subesinghe, S., Hyrich, K. L., & Galloway, J. B. (2018). Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann. Rheum. Dis.*, *77*(6), 905–910. https://doi.org/10.1136/annrheumdis-2017-212825

Sanchez-Piedra, C., Hernández Miguel, M. V., Manero, J., Roselló, R., Sánchez-Costa, J. T., Rodríguez-Lozano, C., Campos, C., Cuende, E., Fernández-Lopez, J. C., Bustabad, S., Martín Domenech, R., Pérez-Pampín, E., Del Pino-Montes, J., Millan-Arciniegas, A. M., Díaz-González, F., Gómez-Reino, J. J., & en representación del Grupo de trabajo BIOBADASER Fase III. (2019). Objectives and methodology of BIOBADASER phase iii. *Reumatol. Clin.*, *15*(4), 229–236. https://doi.org/10.1016/j.reuma.2017.08.001

Schmidt, M., Schmidt, S. A. J., Sandegaard, J. L., Ehrenstein, V., Pedersen, L., & Sørensen, H. T. (2015). The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin. Epidemiol.*, *7*, 449–490. https://doi.org/10.2147/CLEP.S91125

Simard, J. F., Neovius, M., Askling, J., & ARTIS Study Group. (2012). Mortality rates in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: drug-specific comparisons in the Swedish Biologics Register. *Arthritis Rheum.*, *64*(11), 3502–3510. https://doi.org/10.1002/art.34582

Simon, T. A., Thompson, A., Gandhi, K. K., Hochberg, M. C., & Suissa, S. (2015). Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. *Arthritis Res. Ther.*, *17*, 212. https://doi.org/10.1186/s13075-015-0728-9

Smolen, J. S., Aletaha, D., & McInnes, I. B. (2016). Rheumatoid arthritis. *Lancet Lond. Engl.*, *388*(10055), 2023–2038. https://doi.org/10.1016/S0140-6736(16)30173-8

Sokka, T., Kautiainen, H., Pincus, T., Verstappen, S. M. M., Aggarwal, A., Alten, R., Andersone, D., Badsha, H., Baecklund, E., Belmonte, M., Craig-Müller, J., da Mota, L. M. H., Dimic, A., Fathi, N. A., Ferraccioli, G., Fukuda, W., Géher, P., Gogus, F., Hajjaj-Hassouni, N., Hamoud, H., Haugeberg, G., Henrohn, D., Horslev-Petersen, K., Ionescu, R., Karateew, D., Kuuse, R., Laurindo, I. M. M., Lazovskis, J., Luukkainen, R., Mofti, A., Murphy, E., Nakajima, A., Oyoo, O., Pandya, S. C., Pohl, C., Predeteanu, D., Rexhepi, M., Rexhepi, S., Sharma, B., Shono, E.,

Sibilia, J., Sierakowski, S., Skopouli, F. N., Stropuviene, S., Toloza, S., Valter, I., Woolf, A., Yamanaka, H., & QUEST-RA. (2010). Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. *Arthritis Res. Ther.*, *12*(2), R42. https://doi.org/10.1186/ar2951

Strangfeld, A., Listing, J., Herzer, P., Liebhaber, A., Rockwitz, K., Richter, C., & Zink, A. (2009). Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA*, *301*(7), 737–744. https://doi.org/10.1001/jama.2009.146

Wadström, H., Eriksson, J. K., Neovius, M., Askling, J., & ARTIS Study Group. (2015). How good is the coverage and how accurate are exposure data in the Swedish Biologics Register (ARTIS)? *Scand. J. Rheumatol.*, *44*(1), 22–28. https://doi.org/10.3109/03009742.2014.927918

Westhovens, R., Rigby, W. F. C., van der Heijde, D., Ching, D. W. T., Stohl, W., Kay, J., Chopra, A., Bartok, B., Matzkies, F., Yin, Z., Guo, Y., Tasset, C., Sundy, J. S., Jahreis, A., Mozaffarian, N., Messina, O. D., Landewé, R. B., Atsumi, T., & Burmester, G. R. (2021). Filgotinib in combination with methotrexate or as monotherapy versus methotrexate monotherapy in patients with active rheumatoid arthritis and limited or no prior exposure to methotrexate: the phase 3, randomised controlled FINCH 3 trial. *Ann. Rheum. Dis.*, annrheumdis-2020-219213. https://doi.org/10.1136/annrheumdis-2020-219213

# ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

# ANNEX 2. ENCePP CHECKLIST FOR STUDY PROTOCOLS

## 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 (GVP).

| **Study title:** |
|---|
| Non-interventional post-authorization safety study of filgotinib in the treatment of patients with moderate to severe active rheumatoid arthritis within European registries |

| |
|---|
| **EU PAS Register® number:** To de determined<br>**Study reference number (if applicable):** |

| **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] | ☒ | ☐ | ☐ | Section 6 |

[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.

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | Section 6 |
| 1.1.3 Progress report(s) | ☐ | ☒ | ☐ | |
| 1.1.4 Interim report(s) | ☒ | ☐ | ☐ | Section 6 |
| 1.1.5 Registration in the EU PAS Register® | ☒ | ☐ | ☐ | Section 6 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | Section 6 |

Comments:

| |
|---|
| |

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | ☒ | ☐ | ☐ | Section 8 |
| 2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | Section 7 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | Section 8 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | Section 9 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☒ | ☐ | ☐ | Section 9.5 |

Comments:

| |
|---|
| |

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design) | ☒ | ☐ | ☐ | Section 9.1 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | Section 9.1 |
| 3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☒ | ☐ | ☐ | Section 9.7 |
| 3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)) | ☒ | ☐ | ☐ | Section 9.7 |

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

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | Section 9.3<br>Section 9.7 |

Comments:

| |
|---|
| |

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

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) | ☒ | ☐ | ☐ | Section 9.2.6 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☐ | ☒ | ☐ | -- |
| 5.3 Is exposure categorised according to time windows? | ☐ | ☒ | ☐ | -- |
| 5.4 Is intensity of exposure addressed? (e.g. dose, duration) | ☐ | ☒ | ☐ | -- |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 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? | ☒ | ☐ | ☐ | Section 9.2.6 |

Comments:

| |
|---|
| |

| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☒ | ☐ | ☐ | Section 8, Annex 6 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | Annex 6 |
| 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) | ☐ | ☒ | ☐ | -- |
| 6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management) | ☐ | ☐ | ☒ | -- |

Comments:

| |
|---|
| |

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication) | ☒ | ☐ | ☐ | Section 9.2.6<br>Section 9.3.1-5<br>Section 9.3.8 |
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias) | ☐ | ☒ | ☐ | -- |
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☐ | ☒ | ☐ | -- |

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) | ☐ | ☒ | ☐ | -- |

Comments:

| |
|---|
| |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | Section 9.2 |
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | Section 9.2 |
| 9.1.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | Section 9.3 |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | Section 9.2 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | Section 9.2 |
| 9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | Section 9.3 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☐ | ☒ | ☐ | -- |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | ☒ | ☐ | ☐ | Section 9.3<br>Section 9.4<br>Annex 6 |
| 9.3.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | Section 9.3<br>Section 9.4 |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☒ | ☐ | ☐ | Section 9.2 |

Comments:

| |
|---|
| |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Are the statistical methods and the reason for their choice described? | ☒ | ☐ | ☐ | Section 9.7 |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.2 Is study size and/or statistical precision estimated? | ☒ | ☐ | ☐ | Section 9.5 |
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | Section 9.7 |
| 10.4 Are stratified analyses included? | ☒ | ☐ | ☐ | Section 9.3.7.3 |
| 10.5 Does the plan describe methods for analytic control of confounding? | ☒ | ☐ | ☐ | Section 9.7 |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☐ | ☒ | ☐ | -- |
| 10.7 Does the plan describe methods for handling missing data? | ☐ | ☒ | ☐ | -- |
| 10.8 Are relevant sensitivity analyses described? | ☐ | ☒ | ☐ | -- |

Comments:

| |
|---|
| |

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | Section 9.6<br>Section 9.8 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | Section 9.8 |
| 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? | ☐ | ☒ | ☐ | -- |
| 12.1.2 Information bias? | ☐ | ☒ | ☐ | -- |
| 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). | ☐ | ☒ | ☐ | -- |
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates) | ☒ | ☐ | ☐ | Section 9.1<br>Section 9.5 |

Comments:

| |
|---|
| |

| **Section 13: Ethical/data protection issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☒ | ☐ | ☐ | Section 10.2 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☒ | ☐ | ☐ | Section 10.2 |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | Section 10 |

Comments:

| |
|---|
| |

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

Comments:

| |
|---|
| This section has been removed as there are currently no amendments. |

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

Comments:

| |
|---|
| |

Name of the main author of the protocol: PPD

Date:

Signature: _____

# ANNEX 3. ARTIS SEMI-ANNUAL REPORT TEMPLATE

**The Annual/Biannual Data Report Template (Including the Manchester Template) for Semi-annual Adverse Drug Reaction Reports.**

**Annual/Biannual Data Report**

| Table no. | Description | Comment |
|---|---|---|
| 1 | Demographics | Demographic data not included in Table 3a (Manchester template) |
| 1b | Person-years of follow-up and treatment | By sex and treatment indication. |
| 2 | Distribution of AEs by seriousness | |
| 3a-3c | Manchester template | Table 3a describing the surveillance cohort.<br><br>Table 3b with characteristics at first treatment start with the present biologic drug, all patients registered, and patients with Rheumatoid Arthritis (RA) or Polyarthritis (PA).<br><br>Table 3c, incidence rates for selected serious events |
| Excel file | Line listings of AEs recorded as serious | |

**Table 1a. Number of patients ever treated, and currently on drug, by treatment indication**

| | Treatment indication [a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Overall** | **RA** | **JA** | **PA** | **PS** | **AS** | **OT** | **Missing** |
| **Patients ever on drug – n (%)** | | | | | | | | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Male | | | | | | | | | | | | | | | | |
| Female | | | | | | | | | | | | | | | | |
| All | | | | | | | | | | | | | | | | |
| **Patients currently on drug [b] – n (%)** | | | | | | | | | | | | | | | | |
| Male | | | | | | | | | | | | | | | | |
| Female | | | | | | | | | | | | | | | | |
| All | | | | | | | | | | | | | | | | |

a RA=rheumatoid arthritis, JA=juvenile arthritis, PA=polyarthritis, PS=psoriatic arthritis, AS=anchylosing spondylitis, OT=other rheumatic disease
b It is acknowledged that data at time of data lock may be incomplete, and thus information on exposure may lag
Treatment duration months – mean: X; median Y; IQR: Z

## Table 1b. Number of person-years of follow-up and of time on biologic treatment; by sex and treatment indication

| | **Treatment indication[a]** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Person-years *of follow-up*** | **Total** | **RA** | **JA** | **PA** | **PS** | **AS** | **OT** | **MI** |
| Male | | | | | | | | |
| Female | | | | | | | | |
| All | | | | | | | | |
| ***on treatment*** | | | | | | | | |
| Male | | | | | | | | |
| Female | | | | | | | | |
| All | | | | | | | | |

a RA=rheumatoid arthritis, JA=juvenile arthritis, PA=polyarthritis, PS=psoriatic arthritis, AS=anchylosing spondylitis, OT=other rheumatic diseaseTable 2. Distribution of AEs by seriousness, and treatment indication - cumulatively during the follow-up period

| **Report according to a revised version of the Manchester template** | | | |
|---|---|---|---|
| Period of observation | Cumulatively | From | March 10, 1999 |
| | This period | From | 1 June 2014 |
| | | To | 30 November 2014 |

## Table 3a. Variables describing the surveillance cohort

| **Variable** | **N** | **%** |
|---|---|---|
| New treatments | | |
| New treatments in this time period | | |
| Newly recorded treatments before this period | | |
| Previously reported cumulative number of treatments | | |
| Current cumulative number of treatments | | |

| | | | |
|---|---|---|---|
| Cumulative number of treatments by gender | | | |
| | Males | | |
| | Females | | |
| | Unknown | | |
| Cumulative number of patients by gender | | | |
| | Males | | |
| | Females | | |
| | Unknown | | |
| Cumulative Number of patients by Age at registration | | | |
| | <18 | | |
| | 18-34 | | |
| | 35-44 | | |
| | 45-54 | | |
| | 55-64 | | |
| | 65-74 | | |
| | 75+ | | |
| | Unknown | | |
| PYRS - Time on actual biologic therapy | | | |
| | Male | | |
| | Females | | |
| | All | | |
| PYRS - Total follow-up | | | |
| | Male | | |
| | Female | | |
| | All | | |

## Table 3b. Characteristics at first treatment start with the present biologic drug, all patients registered, and patients with Rheumatoid Arthritis (RA) or Polyarthritis (PA)

| Variable | | Mean | SD |
|---|---|---|---|
| Year since diagnosis | | | |
| | | | |
| HAQ among RA or PA patients | | | |
| | Female | | |
| | Male | | |
| | Total | | |
| DAS28 among RA or PA patients | | | |
| | Female | | |
| | Male | | |
| | Total | | |

| | | | |
|---|---|---|---|
| PAIN VAS among RA or PA patients | | | |
| | Female | | |
| | Male | | |
| | Total | | |
| Tender joint count among RA or PA patients | | | |
| | Female | | |
| | Male | | |
| | Total | | |
| Swollen joint count among RA or PA patients | | | |
| | Female | | |
| | Male | | |
| | Total | | |
| CRP among all patients | | | |
| | Female | | |
| | Male | | |
| | Total | | |
| CRP among RA or PA patients | | | |
| | Female | | |
| | Male | | |
| | Total | | |
| ESR among all patients | | | |
| | Female | | |
| | Male | | |
| | Total | | |
| ESR among RA or PA patients | | | |
| | Female | | |
| | Male | | |
| | Total | | |
| Global Health VAS in all patients | | | |
| | Female | | |
| | Male | | |
| | Total | | |
| Global Health VAS in RA or PA patients | | | |
| | Female | | |
| | Male | | |
| | Total | | |
| Ever treated with any other biologics | | | |
| | All | | |

| | | | |
|---|---|---|---|
| | Males | | |
| | Females | | |
| Previously treated with any other biologics | | | |
| | All | | |
| | Males | | |
| | Females | | |

**Bi-annual data report template**

**Date**

| Table no. | Description | Comment |
|---|---|---|
| 1 | Demographics | Demographic data not included in Table 3a (Manchester template) |
| 2 | Distribution of AEs by seriousness* | |
| 3a-3c | Manchester template | Incidence rates for selected serious (cumulative) events listed in Table 3c. |
| Excel file | Line listings of AE in serious reports | |

*Seriousness** In the following descriptions, seriousness is used as a stratification variable in the ICH regulatory-reporting sense. These serious cases include your *lethal, life-threatening, or serious* cases, while mild, and moderate cases are non-serious.

**Table 3c. Cumulative listing and inicdence rate of selected serious adverse event diagnoses.**

| INFECTIONS | | | | |
|---|---|---|---|---|
| AE diagnosis | N | % | Rate per 1000 pyrs | |
| | | | Total | On therapy |
| **Both sexes** | | | | |
| Specified diagnosis in plain English | | | | |
| **Males** | | | | |
| **Females** | | | | |

**Table 3c. Continued**

| CARDIOVASCULAR DISORDERS | | | | |
|---|---|---|---|---|
| AE diagnosis | N | % | Rate per 1000 pyrs | |
| | | | Total | On therapy |
| **Both sexes** | | | | |
| Specified diagnosis in plain English | | | | |
| **Males** | | | | |
| **Females** | | | | |

Table 3c. Continued

HAEMATOLOGICAL DISORDERS

| AE diagnosis | N | % | Rate per 1000 pyrs | |
|---|---|---|---|---|
| | | | Total | On therapy |
| **Both sexes** | | | | |
| Specified diagnosis in plain English | | | | |
| **Males** | | | | |
| **Females** | | | | |

Table 3c. Continued

NEOPLASMS

| AE diagnosis | N | % | Rate per 1000 pyrs | |
|---|---|---|---|---|
| | | | Total | On therapy |
| **Both sexes** | | | | |
| Specified diagnosis in plain English | | | | |
| **Males** | | | | |
| **Females** | | | | |

Table 3c. Continued

NEUROLOGICAL DISORDERS

| AE diagnosis | N | % | Rate per 1000 pyrs | |
|---|---|---|---|---|
| | | | Total | On therapy |
| **Both sexes** | | | | |
| Specified diagnosis in plain English | | | | |
| **Males** | | | | |
| **Females** | | | | |

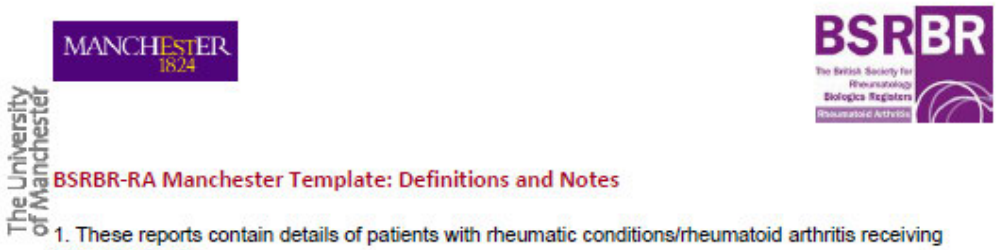
**Line-listing of serious adverse events**

The line-listing is included in a separate Excel spread-sheet. The listing does not include the non-serious events. Below is a description of the variables included.

| Variable | Description |
|---|---|
| new | The value "1" indicates that the event was recorded during the current time period accounted for in the report, and that the event has not been reported on before. |
| changed | The value "1" indicates that the adverse event information included in our data-base has been changed during the current time period. |
| aedate | The date when the adverse event occurred according to the report made by the reporting physician. The format is yyyy-mm-dd (y=year, m=month, d=day) |
| aereport | Each adverse event report is assigned a number. In accordance to the regular adverse drug reporting system in Sweden, each report may include several events (diagnoses). Thus, whenever there are ducplicates of the aereport number, the events stem from the same report. |
| seriousness | Seriousness is used as a stratification variable in the ICH regulatory-reporting sense. The serious events include *lethal, life-threatening,* or *serious* cases. |
| meddrapt | The Swedish regular adverse drug reporting system has not yet joined the international MedDra diagnosing classification, and we cannot other but follow. The events are coded according to the Swedish classification, and then converted to the MedDra preffered term diagnosis code. We follow the Swedish Medical Products Agency (MPA) in this matter, and will update the classification used in concordance with the Agency. |
| recdate | Automatically generated date of the recording of an event. This date is locked and cannot be changed. |
| chadate | Automatically generated date of the most recent change of any information included in a record of an event |
| gender | - |
| age | Age at the recorded date of the adverse event, generated from the date of birth and the "aedate". |
| dob | Date of birth, generated from the Swedish personal identification numbers which persists during a person's whole life, and which can be checked for errors in data entering. |
| class | Averse event diagnosis class according to the Swedish classification. |
| ae | Adverse event diagnosis translated into English using a format received from the Swedish MPA. |
| aecode | The original Swedish adverse event classification code. |
| dxcat | Underlying disease diagnosis class. The disease for which the |

| | |
|---|---|
| | treatment is received. |
| estart, rstart, hstart, or mstart | The date of initiation of the specific biologics treatment |
| debyr | The year of underlying disease debut |
| latency | Number of months from treatment initiation to the recorded date of the adverse event |
| evaluation | Describes the present status of the event report. "Active" reports are not yet completed. |
| swedis | Indicates whether the report also was sent to the regular spontaneous adverse drug reporting system of Sweden |
| association | The evaluation of the association between the biologic drug and the reported event |
| action | The action taken dur to the event |
| course | The course of the event morbidity |
| swedisnumb | The registration number assigned to the event in SWEDIS, the regular spontaneous reporting system in Sweden. |

# ANNEX 4. THE BSRBR-RA MANCHESTER TEMPLATE



## BSRBR-RA Manchester Template: Definitions and Notes

1. These reports contain details of patients with rheumatic conditions/rheumatoid arthritis receiving biologic therapy

2. There is also a report focussing on the appropriate comparison cohort for the above biologic therapy

3. For the purpose of this report, the definition for rheumatoid arthritis is as follows:
*"a diagnosis of RA or ACR criteria ≥4"*

4. Each report is divided into three sections:
(a) demographics
(b) baseline characteristics
(c) crude non-adjusted serious adverse events reported rates

5. When a new drug joins the study, both the Manchester Template and the PSURs will not contain any data until those patients first registered have reached 6 months of follow-up.

6. The data in these reports is truncated at five years. On request, and where appropriate agreements are in place, it is possible to receive an additional report which contains all follow-up data to date (i.e. not truncated at five years).

7. When interpreting the SAE rates, please take note of the following disclaimer:

*The reader should understand that incidence rates presented here reflect interim data from ongoing studies. Therefore, they may be subject to several potential limitations. At the time of reporting, not all AEs or person-time experience may have been completely captured. Also, because of the potential presence of bias, any crude comparisons of incidence rates for the exposed and the non-exposed (comparison) cohorts should be interpreted with caution; for several outcomes of interest, comparisons may be confounded by indication or severity of disease. Crude rates of events show risk of exposure to the biologic therapy for this report and therefore do not take into account biologic exposure prior to registration with BSRBR. At the end of the study, in the statistical analysis, there will be an attempt to adjust for any differences in severity of disease, as well as to adjust for other potential confounders.*

Incidence rates presented here are based on different definitions of the risk window, depending on the outcome of interest:

(1) **For all AEs except malignancy or death (incl. pregnancy)**, the risk window begins with the start of the index biologic agent and continues until 90 days after the end of therapy (or 9 months for rituximab), death or end of data collection, whichever comes first. SAEs, which occur beyond this risk window, will not count for purposes of incidence rate estimation. However, where a patient starts a second biologic agent within 90 days after discontinuing a first one, the risk windows will overlap and both agents will get credit for the SAE. For control patients, follow-up time starts at entry to study and continues until death, the last date of contact or until patient starts a biologic drug.

(2) **For analyses of risk of death**, the risk window begins with the start of the index biologic agent and continues until 90 days after the end of therapy (or 9 months for rituximab), death or the cut-off date for this report (i.e. 30th Nov or 31st May), whichever comes first. Deaths

which occur beyond this risk window, will not count for purposes of incidence rate estimation. For control patients, follow-up time starts at entry to study and continues until death, the cut-off date or patient starts biologic drug.

(3) **For analyses of risk of malignancy**, the risk window for any biologic therapy includes all person-time in the register (since starting that biologic therapy) and extends until the cut-off date for this report (i.e. 30th Nov or 31st May) or date of death whichever occurs sooner, even in case of subsequent switching to another biologic agent. Where a malignancy is diagnosed after a second agent has begun, both agents will receive credit in the incidence rate estimations. For control patients, follow-up time starts at entry to study and continues until death, the cut-off date or patient starts biologic drug.

At the conclusion of the study, incidence rates will be recalculated with complete data, and will reflect appropriate risk windows for the AEs of interest. Cancer incidence rates will also be calculated to reflect the experience of patients who have and have not switched therapies.

## MANCHESTER TEMPLATE – BSRBR-RA 6 MONTHLY REPORT

## PART 1 DEMOGRAPHICS Drug Name

**Cumulative Period of Observation**

**Number of New Drug Name Registrations (##/##/#### to ##/##/####)**

**Cumulative Number of Registrations (since ##/##/####)**

| | |
|---|---|
| **Cumulative Number by Gender** | **Male** |
| | **Female** |
| **Cumulative Number by Age at Registration** | **16-18** |
| | **19-34** |
| | **35-44** |
| | **45-54** |
| | **55-64** |
| | **65-74** |
| | **75+** |

PART 1 DEMOGRAPHICS Drug Name

**SWITCHES**

Cumulative Number of those who have switched to Drug Name (since ##/##/####)

Cumulative Number by Gender
- Male
- Female

Cumulative Number by Age at Registration
- 16-18
- 19-34
- 35-44
- 45-54
- 55-64
- 65-74
- 75+

**DURATION OF FOLLOW-UP**

The total duration of follow-up in person-years:

| | | All Subjects | | Subjects with at least one follow-up | |
|---|---|---|---|---|---|
| Malignancy | Male | | | | |
| | Female | | | | |
| | Total | | | | |
| Death | Male | | | | |
| | Female | | | | |
| | Total | | | | |
| All other outcomes | Male | | | | |
| | Female | | | | |
| | Total | | | | |

## PART 2 BASELINE CHARACTERISTICS Drug Name

Baseline Characteristics of all patients who have EVER received Drug Name

| | | N | Mean | SD |
|---|---|---|---|---|
| Age in years | Male | | | |
| | Female | | | |
| | Total | | | |
| Years since diagnosis | Male | | | |
| | Female | | | |
| | Total | | | |
| HAQ | Male | | | |
| | Female | | | |
| | Total | | | |
| DAS28 | Male | | | |
| | Female | | | |
| | Total | | | |
| TENDER JOINT COUNT | Male | | | |
| | Female | | | |
| | Total | | | |
| SWOLLEN JOINT COUNT | Male | | | |
| | Female | | | |
| | Total | | | |
| ESR | Male | | | |
| | Female | | | |
| | Total | | | |
| CRP | Male | | | |

| | | | | |
|---|---|---|---|---|
| | Female | | | |
| | **Total** | | | |
| **GLOBAL HEALTH VAS** | Male | | | |
| | Female | | | |
| | **Total** | | | |
| **WEIGHT** | Male | | | |
| | Female | | | |
| | **Total** | | | |
| **STEROIDS AT BASELINE** | Male | | | |
| | Female | | | |
| | **Total** | | | |

## PART 3 SERIOUS ADVERSE EVENTS RECORDED Drug Name

[All rates are per 1000 person years with 95% confidence intervals]

| Event | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | Events | Rate (95% CI) | Events | Rate (95% CI) | Events | Rate (95% CI) |
| Total serious infection | | | | | | |
| | | | | | | |
| Pneumonia | | | | | | |
| | | | | | | |
| Septicaemia | | | | | | |
| | | | | | | |
| Septicaemia (site specific infection) | | | | | | |
| | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Bone/Joint infection | | | | | | |
| | | | | | | |
| Opportunistic infection | | | | | | |
| | | | | | | |
| Other serious infection | | | | | | |
| | | | | | | |
| TB | | | | | | |
| | | | | | | |
| **Total cardiac disorders** | | | | | | |
| | | | | | | |
| CHF (new or worsening) | | | | | | |
| | | | | | | |
| Myocardial infarction | | | | | | |
| | | | | | | |
| Other cardiac events | | | | | | |
| | | | | | | |
| **CNS Disorders** | | | | | | |
| | | | | | | |
| Demyelination | | | | | | |
| | | | | | | |
| Peripheral neuropathy | | | | | | |
| | | | | | | |
| Other CNS | | | | | | |
| | | | | | | |
| **Total haematologic events** | | | | | | |
| | | | | | | |
| Aplastic anaemia | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Pancytopaenia | | | | | | |
| Agranulocytosis | | | | | | |
| Other dyscrasia | | | | | | |
| **Total malignant events** | | | | | | |
| Lymphoproliferative | | | | | | |
| Lymphoma (NHL, Hodgkins) | | | | | | |
| Myeloma | | | | | | |
| Leukaemia | | | | | | |
| Non-melanoma skin cancer | | | | | | |
| Other malignant solid tumours | | | | | | |
| Of which, brain neoplasms | | | | | | |
| Of which, glioblastoma | | | | | | |
| Death (90 day risk window) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Death (ever exposed) | | | | | | |
| | | | | | | |
| Pregnancy | | | | | | |
| | | | | | | |

# ANNEX 5. THE RABBIT MANCHESTER TEMPLATE

**19th GERMAN BIOLOGICS REGISTER REPORT – Cohort 2**

REGISTERED DRUG: **XXX®**

A DEMOGRAPHICS

| | | | |
|---|---|---|---|
| **Data source:** | | **RABBIT**: German register for the long-term observation of therapy with biologics in adult patients with RA | |
| | Start of observation | 2007 | |
| 1 | Last period of observation: | From: | May 1, 2016 |
| | | To: | October 31, 2016 |

2a Number of new registrations in last period:

2b Cumulative number of registrations:

3 Cumulative number of patients by gender:

Females
Males

4 Cumulative number by age at registration:

18 – 34
35 – 44
45 – 54
55 – 64
65 – 74
75+

5 Patient years of observation since registration to end of last period (ITT):

Females
Males
Total

6 Number of patients who were under XXX treatment at any time (Patients under Risk):

Females
Males
Total

6a Patient years under XXX treatment (on drug until last given dose plus three months risk window):

Females
Males
Total

6b Patient years since beginning of XXX treatment at any time until end of observation:

Females
Males
Total

Manchester Template 19HJB.docx

B BASELINE CHARACTERISTICS OF PATIENTS REGISTERED

| | Females (n = ) | Males (n = ) | Total (n = ) |
|---|---|---|---|
| Age: mean (SD) | () | () | () |
| Years since symptoms onset: mean (SD)<br>median | ()<br>median: | ()<br>median: | ()<br>median: |
| Global Health VAS: mean (SD)<br>(NRS 0 to 10) | () | () | () |
| Pain VAS: mean (SD)<br>(NRS 0 to 10) | () | () | () |
| FFbH (% of full function by Hannover Functional Status Questionnaire, version polyarthritis and back pain) | () | () | () |
| DAS28: mean (SD)<br>median | ()<br>median: | ()<br>median: | ()<br>median: |
| 28 Tender Joint Count: mean (SD) | () | () | () |
| 28 Swollen Joint Count: mean (SD) | () | () | () |
| CRP: number tested<br>mean (SD)<br>median | n =<br>()<br>median: | n =<br>()<br>median: | n =<br>()<br>median: |
| ESR: number tested<br>mean (SD)<br>median | n =<br>()<br>median: | n =<br>()<br>median: | n =<br>()<br>median: |
| Rheumatoid factor positive: N (%) | (%) | (%) | (%) |
| Dose of Glucocorticoids, average over 6 months: mean (SD) | () | () | () |

B BASELINE CHARACTERISTICS OF PATIENTS REGISTERED

| | Females (n = ) | Males (n = ) | Total (n = ) |
|---|---|---|---|
| Patients with previous Biologics and Biosimilars: N (%) | (%) | (%) | (%) |
| Number of previous Biologics and Biosimilars: mean (SD) | () | () | () |
| Number of previous csDMARDs: mean (SD) | () | () | () |
| No comorbidity: N (%) | (%) | (%) | (%) |
| One comorbidity: N (%) | (%) | (%) | (%) |
| Two comorbidities: N (%) | (%) | (%) | (%) |
| Three or more comorbidities: N (%) | (%) | (%) | (%) |

**List of abbreviations:**

ESR: erythrocyte sedimentation rate (Westergren method)
CRP: C-reactive protein

C1 SERIOUS ADVERSE EVENTS (SAE) observed in patients treated with XXX within the last three months before the occurrence of the SAE (three months slot)

| Event | Cumulative | | Rate/1000 patient years (95% confidence interval) | | |
|---|---|---|---|---|---|
| | Number of SAEs | Percent of Pts. under risk (n =) | Females (p.yrs =) | Males (p.yrs =) | Total (p.yrs =) |
| **Serious infections (excl TB)** | | | | | |
| Pneumonia | 0 (0 F, 0 M) | % | | | |
| Other infections of the respiratory system | 0 (0 F, 0 M) | % | | | |
| Infections of the CNS | 0 (0 F, 0 M) | % | | | |
| Sepsis | 0 (0 F, 0 M) | % | | | |
| Bone or joint infections | 0 (0 F, 0 M) | % | | | |
| Opportunistic infections | 0 (0 F, 0 M) | % | | | |
| Other infections | 0 (0 F, 0 M) | % | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |
| **Tuberculosis** | | | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |
| **Cardiac Disorders** | | | | | |
| Heart failure (incl CHF) | 0 (0 F, 0 M) | % | | | |
| Coronary artery disease | 0 (0 F, 0 M) | % | | | |
| Myocardial infarction | 0 (0 F, 0 M) | % | | | |
| Other cardiac disorders | 0 (0 F, 0 M) | % | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |
| **Hematologic disorders** | | | | | |
| Bone marrow depression and hypoplastic anaemia | 0 (0 F, 0 M) | % | | | |
| Decreased white blood cell | 0 (0 F, 0 M) | % | | | |
| Platelet disorders | 0 (0 F, 0 M) | % | | | |
| Other blood dyscrasia | 0 (0 F, 0 M) | % | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |

C1 SERIOUS ADVERSE EVENTS (SAE) observed in patients treated with XXX within the last three months before the occurrence of the SAE (three months slot)

| Event | Cumulative | | Rate/1000 patient years (95% confidence interval) | | |
|---|---|---|---|---|---|
| | Number of SAEs | Percent of Pts. under risk (n =) | Females (p.yrs =) | Males (p.yrs =) | Total (p.yrs =) |
| **Disorders of the nervous system (excl infections)** | | | | | |
| *Central nervous system:* | | | | | |
| Stroke | 0 (0 F, 0 M) | % | | | |
| Central demyelination | 0 (0 F, 0 M) | % | | | |
| Other disorders of the CNS | 0 (0 F, 0 M) | % | | | |
| *Peripheral nervous system:* | | | | | |
| Disorders of the peripheral nervous system | 0 (0 F, 0 M) | % | | | |
| *Psychiatric disorders:* | | | | | |
| Psychiatric disorders | 0 (0 F, 0 M) | % | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |
| **Allergic conditions and hypersensitivity** | | | | | |
| **TOTAL** | 0 (0 F, 0 M) | % | | | |
| **Hepatic failure** | | | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |
| **Gastrointestinal perforation** | | | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |
| **Pregnancies, Pregnancy of Partner** | | | | | |
| Serious events associated with pregnancies (Abortions, Caesarean section) | 0 (0 F, 0 M) | % | | | |
| **TOTAL Pregnancies** | **0 (0 F, 0 M)** | **%** | | | |

C1 SERIOUS ADVERSE EVENTS (SAE) observed in patients treated with XXX within the last three months before the occurrence of the SAE (three months slot)

| Event | Cumulative | | Rate/1000 patient years (95% confidence interval) | | |
|---|---|---|---|---|---|
| | Number of SAEs | Percent of Pts. under risk (n =) | Females (p.yrs =) | Males (p.yrs =) | Total (p.yrs =) |
| **Operations and hospitalisations** | | | | | |
| Bone and joint surgery and other joint therapeutic procedures | 0 (0 F, 0 M) | % | | | |
| Other operations and (major) therapeutic procedures that lead to hospitalisation | 0 (0 F, 0 M) | % | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |
| **Other serious diagnoses, symptoms and syndromes** | | | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |
| **All Deaths** | | | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |

In Table C1 all SAEs observed in patients treated with XXX within the last three months before the occurrence of the SAE are reported (three months slot). The patients under risk are therefore those patients who were under XXX at any time (n =). The corresponding patient years are given on page 1, item 6.a 'Patient years under XXX treatment (last given dose plus three months risk window)' with years for females, years for males and years in total.

C2 SELECTED SERIOUS ADVERSE EVENTS (SAE) observed in the intention-to-treat (ITT) population

| Event | Cumulative | | Rate/1000 patient years (95% confidence interval) | | |
|---|---|---|---|---|---|
| | Number of SAEs | Percent of Pts. under risk (n = ) | Females (p.yrs = ) | Males (p.yrs = ) | Total (p.yrs = ) |
| **Neoplasms** | | | | | |
| Leukaemia (excl. B-CLL) | 0 (0 F, 0 M) | % | | | |
| Lymphoma (NHL incl. B-CLL, Hodgkin) | 0 (0 F, 0 M) | % | | | |
| Other haematopoietic neoplasm (malignant and benign) | 0 (0 F, 0 M) | % | | | |
| Solid malignancies (all) | 0 (0 F, 0 M) | % | | | |
| thereof Glioblastoma | 0 (0 F, 0 M) | % | | | |
| Benign neoplasms | 0 (0 F, 0 M) | % | | | |
| Unspecified neoplasms and precanceroses | 0 (0 F, 0 M) | % | | | |
| Metastasis, cancer related morbidities, associated syndromes | 0 (0 F, 0 M) | % | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |
| **All Deaths** | | | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |

Table C2 shows all neoplasms and deaths observed in the ITT population (n = ). The corresponding patient years are the years of observation in the ITT population (page 1, item 5) with years for females, years for males and years in total.

C3 SELECTED SERIOUS ADVERSE EVENTS (SAE) observed in patients who were under XXX treatment at any time

| Event | Cumulative | | Rate/1000 patient years (95% confidence interval) | | |
|---|---|---|---|---|---|
| | Number of SAEs | Percent of Pts. under risk (n =) | Females (p.yrs =) | Males (p.yrs =) | Total (p.yrs =) |
| **Neoplasms** | | | | | |
| Leukaemia (excl. B-CLL) | 0 (0 F, 0 M) | % | | | |
| Lymphoma (NHL incl. B-CLL, Hodgkin) | 0 (0 F, 0 M) | % | | | |
| Other haematopoietic neoplasm (malignant and benign) | 0 (0 F, 0 M) | % | | | |
| Solid malignancies (all) | 0 (0 F, 0 M) | % | | | |
| thereof Glioblastoma | 0 (0 F, 0 M) | % | | | |
| Benign neoplasms | 0 (0 F, 0 M) | % | | | |
| Unspecified neoplasms and precanceroses | 0 (0 F, 0 M) | % | | | |
| Metastasis, cancer related morbidities, associated syndromes | 0 (0 F, 0 M) | % | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |
| **All Deaths** | | | | | |
| **TOTAL** | **0 (0 F, 0 M)** | **%** | | | |

Table C3 contains all neoplasms and deaths observed in patients ever treated with XXX before. The corresponding patient years are calculated as from the beginning of XXX therapy to end of observation (page 1, item 6b) with years for females, years for males and years in total.

Disclaimer for the tables above:
The incidence rates presented here reflect interim data from an ongoing study. Therefore, they may be subject to several potential limitations. At the time of reporting, not all SAEs or person-time experience may have been completely captured. Also, because of the potential presence of biases, any crude comparisons of incidence rates for the exposed and the non-exposed (control) cohorts should be interpreted with caution; for several outcomes of interest, comparisons may be confounded by indication or severity of disease. At the end of the study, in the statistical analysis, there will be an attempt to adjust for any differences in severity of disease, as well as to control for other potential confounders.

# ANNEX 6. DEFINITION OF SAFETY ENDPOINTS IN THE EUROPEAN REGISTRIES WITHIN WHICH THE FILGOTINIB POST-AUTHORIZATION SAFETY STUDY WILL BE PERFORMED

| | BSRBR-RA, RABBIT, BIOBADASER | ARTIS, DANBIO |
|---|---|---|
| **Safety Risk** | **Operationalization (MedDRA* code draft list; final list to be defined based on reported endpoints in each registry)** | **Operationalization** |
| Serious and opportunistic infections | Hospitalization and/or use of parenteral antibiotics + MedDRA Infections and Infestations SOC 10021881. | Hospitalizations in the Patient Register listing as main diagnosis ICD10-codes below. If main diagnosis is RA, contributory diagnoses are also considered. A00-B99 (excluding A33 and A50), D73.3, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J39.0-J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00-L08, L30.3, M00-M01, M46.2-M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N13.6, N15.1, N15.9, N30.0 N30.8, N34.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1. |
| Herpes zoster/ Varicella zoster | 10019974 Herpes zoster, 10019983 Herpes zoster ophthalmic, 10030865 Ophthalmic herpes zoster, 10058428 Herpes zoster multi-dermatomal, 10063491 Herpes zoster oticus, 10065038 Herpes zoster disseminated, 10065119 Necrotising herpetic retinopathy, 10072210 Genital herpes zoster, 10074241 Varicella zoster gastritis, 10074245 Herpes zoster pharyngitis, 10074248 Herpes zoster meningoencephalitis, 10074253 Herpes zoster necrotising retinopathy, 10074254 Varicella zoster pneumonia, 10074254 Varicella zoster pneumonia, 10074259 Herpes zoster meningitis, 10074297 Herpes zoster cutaneous disseminated. | Hospitalizations in the Patient Register listing as main diagnosis ICD10-codes A02, A15-A19, A31, A32, A43, A48.1, B02, B38, B39, B40, B44, B45, B58, B59. If main diagnosis is RA, contributory diagnoses are also considered. |
| Malignancy | Malignant or unspecified tumours. | All invasive malignancies recorded in the cancer register, excluding NMSC. |
| Non-melanoma skin cancer (NMSC) | 10004146 Basal cell carcinoma; 10004178 Basosquamous carcinoma; 10004179 Basosquamous carcinoma of skin; 10006059 Bowen's disease; 10007390 Carcinoma in situ of skin; 10064055 Lip squamous cell carcinoma; 10063693 Malignant neoplasm of eyelid; 10040808 Skin cancer; 10055115 Skin cancer metastatic 10041834 Squamous cell carcinoma of skin. | Identified through the Cancer register as all malignancies with ICD-O/2 code C44 and D04, plus ICD7 code 191, and all basal cell cancers recoded in the register's subcomponent on basal cell cancers. |

| Safety Risk | BSRBR-RA, RABBIT, BIOBADASER<br>Operationalization (MedDRA* code draft list; final list to be defined based on reported endpoints in each registry) | ARTIS, DANBIO<br>Operationalization |
|---|---|---|
| Gastrointestinal (GI) perforation | 10000099 Abdominal wall abscess; 10000285 Abscess intestinal; 10000582 Acquired tracheo-oesophageal fistula; 10002156 Anal fistula; 10002157 Anal fistula excision; 10002248 Anastomotic ulcer perforation; 10002924 Aorto-duodenal fistula; 10003012 Appendicitis perforated; 10009995 Colonic fistula; 10013536 Diverticular fistula; 10013538 Diverticulitis; 10013541 Diverticulitis intestinal haemorrhagic; 10013828 Duodenal fistula; 10013832 Duodenal perforation; 10013849 Duodenal ulcer perforation; 10013849 Duodenal ulcer perforation; 10013850 Duodenal ulcer perforation, nonobstructive; 10017815 Gastric perforation; 10017835 Gastric ulcer perforation; 10017836 Gastric ulcer perforation, obstructive; 10017866 Gastritis haemorrhagic; 10017877 Gastrointestinal fistula; 10017954 Gastrointestinal gangrene; 10017955 Gastrointestinal haemorrhage; 10018001 Gastrointestinal perforation; 10021305 Ileal perforation; 10021310 Ileal ulcer perforation; 10022647 Intestinal fistula; 10022694 Intestinal perforation; 10023174 Jejunal perforation; 10023178 Jejunal ulcer perforation; 10023804 Large intestine perforation; 10030181 Oesophageal perforation; 10034354 Peptic ulcer perforation; 10034358 Peptic ulcer perforation, obstructive; 10034397 Perforated peptic ulcer oversewing; 10034649 Peritoneal abscess; 10034674 Peritonitis; 10038073 Rectal perforation; 10038975 Retroperitoneal abscess; 10041103 Small intestinal perforation; 10046274 Upper gastrointestinal haemorrhage; 10048946 Anal abscess; 10048947 Rectal abscess; 10049583 Douglas' abscess; 10049764 Appendiceal abscess; 10050362 Anovulvar fistula; 10050953 Lower gastrointestinal haemorrhage; 10051425 Enterocutaneous fistula; 10052211 Oesophageal rupture; 10052457 Perineal abscess; 10052488 Oesophageal ulcer perforation; 10052814 Perirectal abscess; 10052931 Colon fistula repair; 10052991 Intestinal fistula repair; 10053267 Rectal fistula repair; 10056086 Paraoesophageal abscess; 10056346 Anastomotic haemorrhage; 10056991 Enterocolonic fistula; 10056992 Oesophagobronchial fistula; 10058381 Oesophageal fistula repair; 10059175 Intestinal haemorrhage; 10060921 Abdominal abscess; 10061248 Intestinal ulcer perforation; 10061249 Intra-abdominal haemorrhage; 10061820 Diverticular perforation; 10061975 Gastrointestinal ulcer perforation; 10062065 Perforated ulcer; 10062070 Peritonitis bacterial; 10062570 Enterovesical fistula; 10065713 Gastric fistula; 10065879 Gastrointestinal anastomotic leak; 10066870 Aorto-oesophageal fistula; 10066892 Rectourethral fistula; 10067091 Gastropleural fistula; 10068792 Gastrosplenic fistula; 10071647 Infectious peritonitis. | Main diagnosis recorded in the inpatient component of the Patient Register listing ICD10-codes: K22.3, K25.1, K25.2, K25.5, K25.6, K26.1, K26.2, K26.5, K26.6, K27.1, K27.2, K27.5, K27.6, K28.1, K28.2, K28.5, K28.6, K31.6, K35.0, K35.1, K57.0, K57.2, K57.4, K57.8, K63.0, K63.1, K63.2.<br>If main diagnosis is RA (ICD10 codes M05, M06.0, M06.2, M06.3, M06.8, M06.9, M12.3), contributory diagnoses are also allowed. |

| Safety Risk | BSRBR-RA, RABBIT, BIOBADASER<br>Operationalization (MedDRA* code draft list; final list to be defined based on reported endpoints in each registry) | ARTIS, DANBIO<br>Operationalization |
|---|---|---|
| MACE | Fatal and non-fatal : 10000891 Acute myocardial infarction; 10006147 Brain stem infarction; 10006148 Brain stem ischaemia; 10008034 Cerebellar infarction; 10008088 Cerebral artery embolism; 10008120 Cerebral ischaemia; 10008190 Cerebrovascular accident; 10014498 Embolic stroke; 10019005 Haemorrhagic cerebral infarction; 10019016 Haemorrhagic stroke; 10024033 Lateral medullary syndrome; 10028596 Myocardial infarction; 10028602 Myocardial necrosis; 10033697 Papillary muscle infarction; 10043647 Thrombotic stroke; 10049768 Silent myocardial infarction; 10051078 Lacunar infarction; 10055677 Haemorrhagic transformation stroke; 10056237 Migrainous infarction; 10059613 Stroke in evolution; 10060839 Embolic cerebral infarction; 10060840 Ischaemic cerebral infarction; 10061256 Ischaemic stroke; 10062573 Brain stem thrombosis; 10064961 Thalamic infarction; 10066591 Post procedural stroke; 10066592 Post procedural myocardial infarction; 10067167 Cerebellar embolism; 10067347 Thrombotic cerebral infarction; 10067462 Millard-Gubler syndrome; 10068621 Cerebellar ischaemia; 10068644 Brain stem stroke; 10069020 Basal ganglia infarction; 10070671 Cerebral septic infarct; 10070754 Inner ear infarction; 10071043 Basal ganglia stroke; 10071260 Carotid angioplasty; 10073945 Perinatal stroke; 10074422 Brain stem embolism.<br>Fatal only: 10002886 Aortic aneurysm rupture; 10003173 Arterial rupture; 10003210 Arteriosclerosis; 10003212 Arteriosclerosis moenckeberg-type; 10006145 Brain stem haemorrhage; 10007522 Cardiac asthma; 10007554 Cardiac failure; 10007556 Cardiac failure acute; 10007558 Cardiac failure chronic; 10007559 Cardiac failure congestive; 10007559 Cardiac failure congestive; 10007560 Cardiac failure high output; 10007625 Cardiogenic shock; 10007684 Carotid arterial embolus; 10007686 Carotid artery aneurysm; 10007688 Carotid artery thrombosis; 10008023 Cerebellar artery thrombosis; 10008030 Cerebellar haemorrhage; 10008076 Cerebral aneurysm ruptured syphilitic; 10008086 Cerebral arteriovenous malformation haemorrhagic; 10008089 Cerebral artery occlusion; 10008092 Cerebral artery thrombosis; 10008111 Cerebral haemorrhage; 10008118 Cerebral infarction; 10008132 Cerebral thrombosis; 10018985 Haemorrhage intracranial; 10022758 Intracranial aneurysm; 10022840 Intraventricular haemorrhage; 10022841 Intraventricular haemorrhage neonatal; 10024119 Left ventricular failure; 10024242 Leriche syndrome; 10034476 Pericardial haemorrhage; 10036511 Precerebral artery occlusion; 10039163 Right ventricular failure; 10039330 Ruptured cerebral aneurysm; 10042316 Subarachnoid haemorrhage; 10042434 Sudden death; 10047279 Ventricle rupture; 10048380 Aneurysm ruptured; 10048761 Atrial rupture; 10049418 Sudden cardiac death; 10049993 Cardiac death; 10050403 Carotid artery dissection; 10051093 Cardiopulmonary failure; 10051328 Carotid aneurysm rupture; 10052019 Femoral artery occlusion; 10053633 Cerebellar artery occlusion; 10053649 Vascular rupture; 10053949 Vascular pseudoaneurysm ruptured; 10055803 Haemorrhage coronary artery; 10058178 Aortic occlusion; 10060874 Aortic | Combines MI, stroke, and fatal cardiovascular events: I00-I99 as main cause of death, or I20.0, I21, I60-I64 as diagnosis in in- or outpatient care. |

| Safety Risk | BSRBR-RA, RABBIT, BIOBADASER<br>Operationalization (MedDRA* code draft list; final list to be defined based on reported endpoints in each registry) | ARTIS, DANBIO<br>Operationalization |
|---|---|---|
| | rupture; 10060953 Ventricular failure; 10060964 Arterial haemorrhage; 10062585 Peripheral arterial occlusive disease; 10062599 Arterial occlusive disease; 10063081 Acute left ventricular failure; 10063082 Acute right ventricular failure; 10063083 Chronic left ventricular failure; 10063084 Chronic right ventricular failure; 10064595 Haemorrhagic arteriovenous malformation; 10064601 Iliac artery occlusion; 10065441 Venous haemorrhage; 10065558 Aortic arteriosclerosis; 10067057 Basal ganglia haemorrhage; 10067116 Carotid arteriosclerosis; 10068119 Aortic dissection rupture; 10068119 Aortic dissection rupture; 10068230 Cardiorenal syndrome; 10069694 Brachiocephalic artery occlusion; 10069695 Subclavian artery occlusion; 10069696 Coeliac artery occlusion;10071716 Vertebral artery dissection; 10072043 Central nervous system haemorrhage; 10072789 Iliac artery rupture; 10073565 Intracranial artery dissection; 10073565 Intracranial artery dissection; 10073681 Epidural haemorrhage; 10075449 Brachiocephalic arteriosclerosis; 10076203 Radiation associated cardiac failure. | |
| Venous thromboembolism (deep venous thrombosis and pulmonary embolism) | 10037377 Pulmonary embolism; 10051055 Deep vein thrombosis; 10061408 Venous thrombosis limb; 10063909 Post procedural pulmonary embolism; 10066881 Deep vein thrombosis postoperative. | Main diagnosis in the Patient Register, in- or out-patient component, of the following ICD-10 codes: I26.9, 126.0, I80.1, I80.2, I80.3, I80.8, I80.9, I81.0, I82.0, I82.1, I82.2, I82.3, I82.8, I82.9. Or, pulmonary embolism 126.0 listed as the underlying cause of death. |
| Hyperlipidemia | BIOBADASER: Lipid measures LDL, HDL, total cholesterol or triglycerides may be captured according to clinical practice.<br>BSRBR-RA: Patients who will initiate treatment with statins or other lipid lowering drugs.<br>RABBIT: Hyperlipidemia reported as adverse event by the treating physician. | Patients who will initiate treatment with statins or other lipid lowering drugs. |

* In BIOBADASER MedDRA version 19 is used. Codes could be different to the ones listed here

# ANNEX 7. LIST OF COVARIATES TO BE CONSIDERED AS POTENTIAL CONFOUNDING VARIABLES BY SAFETY OUTCOME OF INTEREST

**Table 4 Potential confounding factors by safety outcome of interest (depending on availability of specific variable by individual registry)**

| *Variable* | SOI | H. zoster /varicella | MACE | VTE (including DVT and PE) | Hyperlipidemia | Malignancy | NMSC | GI perforation | Death |
|---|---|---|---|---|---|---|---|---|---|
| *Key patient characteristics* | | | | | | | | | |
| Age (year of birth) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Sex | ✓ | | ✓ | | ✓ | ✓ | ✓ | | |
| Race | | ✓ | ✓ | | | ✓ | ✓ | | |
| Smoking | ✓ | | ✓ | ✓ | ✓ | ✓ | | | ✓ |
| Alcohol | | | ✓ | | | ✓ | | | |
| Obesity/BMI | | | ✓ | ✓ | ✓ | ✓ | | | |
| *Co-morbidities (previous/recent diagnosis of)* | | | | | | | | | |
| Serious and opportunistic infections | ✓ | | | | | | | | |
| Herpes zoster and primary Varicella infection | | ✓ | | | | | | | |

| *Variable* | SOI | H. zoster /varicella | MACE | VTE (including DVT and PE) | Hyperlipidemia | Malignancy | NMSC | GI perforation | Death |
|---|---|---|---|---|---|---|---|---|---|
| CVD or stroke | | | ✓ | | | | | | |
| VTE (including DVT, PE) | | | | ✓ | | | | | |
| Hyperlipidemia | | | ✓ | | | | | | |
| Malignancies (excluding NMSC) | | | | ✓ | | ✓ | | | |
| NMSC | | | | | | | ✓ | | |
| GI perforation | | | | | | | | ✓ | |
| Diabetes mellitus | ✓ | | ✓ | | ✓ | | | | |
| Atrial fibrillation | | | ✓ | | | | | | |
| Chronic kidney disease | ✓ | | ✓ | | ✓ | | | | |
| Family history of CVD | | | ✓ | | | | | | |
| Hyperlipidemia | | | ✓ | | | | | | |
| Hypertension | | | ✓ | | ✓ | | | | |
| Rheumatoid arthritis (activity/severity) | ✓ | ✓ | ✓ | | ✓ | | | | |
| Active cancer | | | | ✓ | | ✓ | | | |

| *Variable* | SOI | H. zoster /varicella | MACE | VTE (including DVT and PE) | Hyperlipidemia | Malignancy | NMSC | GI perforation | Death |
|---|---|---|---|---|---|---|---|---|---|
| Known thrombophilic condition | | | | ✓ | | | | | |
| Reduced mobility / hospitalization | | | | ✓ | | | | | |
| Trauma and/or surgery | | | | ✓ | | | | | |
| Ongoing hormonal replacement therapy | | | | ✓ | | | | | |
| Heart and/or respiratory failure | | | | | | | | | |
| Acute myocardial infarction or ischemic stroke | | | | ✓ | | | | | |
| Acute infection and/or rheumatologic disorder | | | | ✓ | | | | | |
| Chronic lung disease | ✓ | | | | | | | | |
| Prior DMARD treatment failure | ✓ | | | | | | | | |
| Glucocorticoid | ✓ | ✓ | | | | | | ✓ | |
| TNFα inhibitors | ✓ | | | | | | | | |
| Other immunosuppressant/modifying therapy | ✓ | | | | | | ✓ | | |
| Thiopurines | | ✓ | | | | | | | |

| *Variable* | SOI | H. zoster /varicella | MACE | VTE (including DVT and PE) | Hyperlipidemia | Malignancy | NMSC | GI perforation | Death |
|---|---|---|---|---|---|---|---|---|---|
| Combination therapy | | | | | | | | | |
| NSAIDs | | | | | | | | ✓ | |
| History of diverticulitis | | | | | | | | ✓ | |
| Other GI conditions | | | | | | | | ✓ | |
| Phototherapy | | | | | | | ✓ | | |
| Diet | | | ✓ | | ✓ | | | | |
| Inactivity | | | ✓ | | ✓ | | | | |
| Biliary obstruction | | | | | ✓ | | | | |
| Hypothyroidism | | | | | ✓ | | | | |
| Familial hypercholesterolemia | | | | | ✓ | | | | |
| Family history of cancer | | | | | | ✓ | | | |

BMI = body mass index; SOI = serious opportunistic infection; Hx = history; NA = not applicable

# ANNEX 8. POWER (%) TO DETECT AN INCREASE IN THE RISK OF DEVELOPING AN ADVERSE EVENT IN PATIENTS EXPOSED TO FILGOTINIB COMPARED TO PATIENTS ON BDMARDS (A = 0.05)

| | | | bDMARD-exposed Patients (N) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2-year Average Follow-up | | | 3-year Average Follow-up | | | 5-year average Follow-up | | |
| **Estimated Risk** | **RR** | **Filgotinib-exposed Patients (N)** | **2000** | **5000** | **10000** | **2000** | **5000** | **10000** | **2000** | **5000** | **10000** |
| Risk with rate 40/1000 PY | 1.2 | 300 | 14.5 | 15.3 | 15.6 | 19.4 | 20.6 | 21.1 | 29.2 | 31.2 | 31.9 |
| | | 500 | 19.7 | 21.8 | 22.6 | 27.2 | 30.3 | 31.4 | 41.5 | 46.1 | 47.8 |
| | | 1000 | 29.7 | 35.7 | 38.4 | 41.5 | 49.7 | 53.2 | 61.6 | 71.2 | 74.9 |
| | 1.3 | 300 | 25.9 | 27.7 | 28.3 | 36.2 | 38.7 | 39.6 | 54.5 | 57.9 | 59.1 |
| | | 500 | 36.8 | 40.9 | 42.5 | 51.1 | 56.3 | 58.3 | 72.8 | 78.1 | 80 |
| | | 1000 | 55.4 | 64.9 | 68.7 | 72.8 | 81.9 | 85 | 91.2 | 96 | 97.2 |
| | 1.4 | 300 | 40.4 | 43.1 | 44.2 | 55.6 | 59 | 60.3 | 77.4 | 80.7 | 81.8 |
| | | 500 | 56.5 | 62 | 64 | 73.9 | 79.2 | 81 | 91.9 | 94.7 | 95.6 |
| | | 1000 | 78.3 | 86.6 | 89.3 | 91.9 | 96.4 | 97.5 | 99.1 | 99.8 | 99.9 |
| | 1.5 | 300 | 55.8 | 59.3 | 60.5 | 73.2 | 76.6 | 77.8 | 91.5 | 93.4 | 94.1 |
| | | 500 | 74.2 | 79.4 | 81.2 | 89.2 | 92.6 | 93.6 | 98.5 | 99.3 | 99.4 |
| | | 1000 | 92 | 96.4 | 97.6 | 98.5 | 99.6 | 99.8 | 100 | 100 | 100 |
| | 2 | 300 | 97.4 | 98.2 | 98.5 | 99.8 | 99.9 | 99.9 | 100 | 100 | 100 |
| | | 500 | 99.8 | 99.9 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| | | 1000 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| | 3 | 300 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| | | 500 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| | | 1000 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Risk with rate 10/1000 PY | 1.2 | 300 | 7.2 | 7.4 | 7.5 | 8.4 | 8.7 | 8.8 | 10.7 | 11.2 | 11.3 |
| | | 500 | 8.4 | 8.9 | 9.1 | 10.2 | 10.9 | 11.2 | 13.8 | 15 | 15.5 |
| | | 1000 | 10.8 | 12.3 | 13 | 13.8 | 16 | 17.1 | 19.8 | 23.6 | 25.3 |
| | 1.3 | 300 | 9.9 | 10.3 | 10.5 | 12.4 | 13 | 13.3 | 17.5 | 18.6 | 19 |
| | | 500 | 12.5 | 13.6 | 14 | 16.4 | 18 | 18.7 | 24.3 | 27 | 28 |
| | | 1000 | 17.7 | 21 | 22.5 | 24.3 | 29.2 | 31.3 | 37 | 44.4 | 47.7 |
| | 1.4 | 300 | 13.4 | 14.2 | 14.4 | 17.8 | 18.9 | 19.3 | 26.5 | 28.4 | 29 |
| | | 500 | 18.1 | 19.9 | 20.6 | 24.8 | 27.5 | 28.6 | 37.8 | 42 | 43.6 |
| | | 1000 | 27 | 32.5 | 34.9 | 37.8 | 45.4 | 48.6 | 56.7 | 66.3 | 70 |

| | | | bDMARD-exposed Patients (N) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2-year Average Follow-up | | | 3-year Average Follow-up | | | 5-year average Follow-up | | |
| **Estimated Risk** | **RR** | **Filgotinib-exposed Patients (N)** | **2000** | **5000** | **10000** | **2000** | **5000** | **10000** | **2000** | **5000** | **10000** |
| | 1.5 | 300 | 17.8 | 19 | 19.4 | 24.4 | 26.1 | 26.7 | 37.2 | 39.8 | 40.8 |
| | | 500 | 24.9 | 27.6 | 28.7 | 34.7 | 38.6 | 40.1 | 52.5 | 57.8 | 59.8 |
| | | 1000 | 37.9 | 45.5 | 48.8 | 52.5 | 61.9 | 65.6 | 74.3 | 83.1 | 86.2 |
| | 2 | 300 | 47.9 | 51 | 52.2 | 64.6 | 68.2 | 69.4 | 85.4 | 88.1 | 89 |
| | | 500 | 65.6 | 71.1 | 73.1 | 82.4 | 86.9 | 88.4 | 96.2 | 97.8 | 98.3 |
| | | 1000 | 86.2 | 92.6 | 94.5 | 96.2 | 98.7 | 99.2 | 99.8 | 100 | 100 |
| | 3 | 300 | 92.2 | 94 | 94.6 | 98.5 | 99.1 | 99.2 | 100 | 100 | 100 |
| | | 500 | 98.7 | 99.4 | 99.5 | 99.9 | 100 | 100 | 100 | 100 | 100 |
| | | 1000 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Risk with rate 5/1000 PY | 1.2 | 300 | 6.1 | 6.2 | 6.2 | 6.7 | 6.8 | 6.9 | 7.8 | 8 | 8.1 |
| | | 500 | 6.7 | 6.9 | 7 | 7.6 | 7.9 | 8 | 9.3 | 9.9 | 10.1 |
| | | 1000 | 7.8 | 8.6 | 8.9 | 9.3 | 10.4 | 10.9 | 12.2 | 14.1 | 14.9 |
| | 1.3 | 300 | 7.4 | 7.6 | 7.7 | 8.6 | 8.9 | 9 | 11.1 | 11.6 | 11.8 |
| | | 500 | 8.7 | 9.2 | 9.4 | 10.6 | 11.4 | 11.7 | 14.4 | 15.8 | 16.3 |
| | | 1000 | 11.2 | 12.8 | 13.6 | 14.4 | 16.9 | 18 | 20.9 | 25 | 26.8 |
| | 1.4 | 300 | 9.1 | 9.5 | 9.6 | 11.2 | 11.8 | 12 | 15.5 | 16.5 | 16.8 |
| | | 500 | 11.4 | 12.3 | 12.6 | 14.7 | 16 | 16.6 | 21.3 | 23.6 | 24.5 |
| | | 1000 | 15.8 | 18.6 | 19.8 | 21.3 | 25.5 | 27.4 | 32.3 | 38.9 | 41.8 |
| | 1.5 | 300 | 11.3 | 11.8 | 12 | 14.5 | 15.3 | 15.6 | 21 | 22.4 | 22.9 |
| | | 500 | 14.7 | 16.1 | 16.6 | 19.7 | 21.8 | 22.6 | 29.7 | 33 | 34.3 |
| | | 1000 | 21.4 | 25.6 | 27.5 | 29.7 | 35.7 | 38.4 | 45.3 | 53.9 | 57.5 |
| | 2 | 300 | 26.9 | 28.8 | 29.5 | 37.6 | 40.3 | 41.2 | 56.5 | 59.9 | 61.2 |
| | | 500 | 38.3 | 42.6 | 44.2 | 53.1 | 58.4 | 60.3 | 74.8 | 80 | 81.8 |
| | | 1000 | 57.4 | 67 | 70.8 | 74.8 | 83.6 | 86.7 | 92.4 | 96.7 | 97.7 |
| | 2.5 | 300 | 47 | 50.2 | 51.3 | 63.6 | 67.2 | 68.4 | 84.6 | 87.4 | 88.3 |
| | | 500 | 64.6 | 70.1 | 72.1 | 81.6 | 86.2 | 87.7 | 95.8 | 97.6 | 98.1 |
| | | 1000 | 85.4 | 92.1 | 94.1 | 95.8 | 98.5 | 99.1 | 99.7 | 100 | 100 |
| | 3 | 300 | 66.1 | 69.7 | 70.9 | 82.9 | 85.8 | 86.8 | 96.4 | 97.5 | 97.8 |
| | | 500 | 83.7 | 88 | 89.4 | 95 | 97 | 97.6 | 99.6 | 99.9 | 99.9 |
| | | 1000 | 96.7 | 98.9 | 99.3 | 99.6 | 99.9 | 100 | 100 | 100 | 100 |

| | | | bDMARD-exposed Patients (N) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2-year Average Follow-up | | | 3-year Average Follow-up | | | 5-year average Follow-up | | |
| **Estimated Risk** | **RR** | **Filgotinib-exposed Patients (N)** | **2000** | **5000** | **10000** | **2000** | **5000** | **10000** | **2000** | **5000** | **10000** |
| Risk with rate 1/1000 PY | 1.2 | 300 | 5.2 | 5.2 | 5.2 | 5.3 | 5.4 | 5.4 | 5.5 | 5.6 | 5.6 |
| | | 500 | 5.3 | 5.4 | 5.4 | 5.5 | 5.6 | 5.6 | 5.8 | 6 | 6 |
| | | 1000 | 5.6 | 5.7 | 5.8 | 5.8 | 6.1 | 6.1 | 6.4 | 6.8 | 6.9 |
| | 1.3 | 300 | 5.5 | 5.5 | 5.5 | 5.7 | 5.8 | 5.8 | 6.2 | 6.3 | 6.3 |
| | | 500 | 5.7 | 5.8 | 5.9 | 6.1 | 6.2 | 6.3 | 6.8 | 7.1 | 7.2 |
| | | 1000 | 6.2 | 6.5 | 6.7 | 6.8 | 7.3 | 7.5 | 8.1 | 8.8 | 9.2 |
| | 1.4 | 300 | 5.8 | 5.9 | 5.9 | 6.2 | 6.3 | 6.4 | 7 | 7.2 | 7.3 |
| | | 500 | 6.2 | 6.4 | 6.5 | 6.9 | 7.1 | 7.2 | 8.1 | 8.6 | 8.7 |
| | | 1000 | 7.1 | 7.6 | 7.8 | 8.1 | 8.9 | 9.3 | 10.3 | 11.6 | 12.2 |
| | 1.5 | 300 | 6.2 | 6.3 | 6.4 | 6.8 | 7 | 7 | 8.1 | 8.3 | 8.4 |
| | | 500 | 6.9 | 7.1 | 7.2 | 7.8 | 8.2 | 8.4 | 9.7 | 10.4 | 10.7 |
| | | 1000 | 8.1 | 8.9 | 9.3 | 9.7 | 11 | 11.5 | 13 | 15.1 | 16 |
| | 2 | 300 | 9.2 | 9.6 | 9.7 | 11.4 | 11.9 | 12.1 | 15.7 | 16.7 | 17 |
| | | 500 | 11.5 | 12.4 | 12.8 | 14.9 | 16.2 | 16.8 | 21.6 | 23.9 | 24.9 |
| | | 1000 | 16 | 18.8 | 20.1 | 21.6 | 25.9 | 27.8 | 32.8 | 39.5 | 42.4 |
| | 2.5 | 300 | 13.4 | 14.1 | 14.4 | 17.7 | 18.8 | 19.3 | 26.4 | 28.3 | 28.9 |
| | | 500 | 18 | 19.9 | 20.6 | 24.7 | 27.4 | 28.5 | 37.7 | 41.8 | 43.5 |
| | | 1000 | 26.9 | 32.4 | 34.8 | 37.7 | 45.2 | 48.5 | 56.5 | 66.1 | 69.9 |
| | 3 | 300 | 18.5 | 19.7 | 20.1 | 25.4 | 27.2 | 27.8 | 38.7 | 41.4 | 42.4 |
| | | 500 | 25.9 | 28.7 | 29.8 | 36.2 | 40.2 | 41.8 | 54.5 | 59.8 | 61.8 |
| | | 1000 | 39.5 | 47.3 | 50.6 | 54.5 | 64 | 67.7 | 76.3 | 84.9 | 87.8 |

bDMARD = biologic disease-modifying antirheumatic drug; RR = relative risk; PY = person-years

# SIGNATURE PAGE – INVESTIGATOR

**Study Title:** Non-interventional post-authorization safety study of filgotinib in the treatment of patients with moderate to severe active rheumatoid arthritis within European registries

**Protocol Version:** 1.0 **Date**: {20-Jan-2022}

I, the undersigned, have read this non-interventional study protocol and will conduct the study as described in compliance with the study protocol, in accordance with the guidelines of Good Pharmacoepidemiology Practises and Heads of Medicines Agencies Good Pharmacovigilance Practises.

| Investigator Name | Signature | Date |
|---|---|---|

# SIGNATURE PAGE – SPONSOR

**Study Title:** Non-interventional post-authorization safety study of filgotinib in the treatment of patients with moderate to severe active rheumatoid arthritis within European registries

**Protocol Version:** 1.0 **Date**: {20-Jan-2022}

This clinical study protocol has been reviewed and approved by the sponsor to ensure compliance with guidelines of Good Pharmacoepidemiology Practises and Heads of Medicines Agencies Good Pharmacovigilance Practises.

An electronic signature of the sponsor is provided at the end of the document

| Medical Leader | Signature | Date |
|---|---|---|

Signature Page for glpg0634-cl-403-protocol 21234

| | |
|---|---|
| Approval | PPD ogy Leader<br>Medical Safety<br>20-Jan-2022 11:14:22 GMT+0000 |

| | |
|---|---|
| Approval | PPD erson for Pharmacovigilance<br>Medical Safety<br>20-Jan-2022 11:16:12 GMT+0000 |

Signature Page for glpg0634-cl-403-protocol43952_40911_63355