NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Project Number:	GLPG0634		
Study Number:	GLPG0634-CL-408 (previously: GS-EU-417-9051)		
Study Title:	Non-interventional post-authorization cohort safety study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca®) use in patients with moderate to severe active rheumatoid arthritis within European registries		
Development Phase:	4		
Status:	Final		
Version:	1.0	Date:	2-Feb-2022
EU PAS Register No:	To be determined	ClinicalTrials.gov identifieur:	Not applicable
Active Substance			
Medicinal Product		Product Reference	EU/1/20/1480
Procedure Number	EMEA/H/C/005113/MEA-011-015		
Joint PASS	No		
Research Question and Objectives	To evaluate the effectiveness of the additional risk minimization measures for filgotinib use in patients with rheumatoid arthritis who initiate treatment with filgotinib		
Country (-ies) of study	Denmark, Germany, Spain, Sweden, United Kingdom		
Author/ Contact person	Name: PPD Email: PPD		
Marketing Authorization Holder	Galapagos NV, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium		
MAH contact person	Name: PPD Email: PPD		

Confidentiality Statement

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACR	American College of Rheumatology
ADR	Adverse drug reaction
AE	Adverse event
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
aRMM	Additional risk minimization measure
ARTIS	Anti-Rheumatic Treatment in Sweden
ATC	Anatomical Therapeutic Classification System
BIOBADASER	Spanish Registry of Adverse Events of Biological Therapies in Rheumatoid Diseases (Registro Español de Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas)
BMI	Body mass index
BSR	British Society for Rheumatology
BSRBR-RA	British Society for Rheumatology Biologics Register-Rheumatoid Arthritis
CI	Confidence interval
CrCl	Creatinine clearance
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
CVD	Cardiovascular diseases
DANBIO	Danish Nationwide Clinical Register for Patients with Rheumatoid Arthritis
DAS(28)	Disease activity score (for 28 joint count)
DMARD	Disease-modifying antirheumatic drug
DRFZ	Deutsches Rheuma Forschungszentrum (German Rheumatism Research Center)
DUS	Drug utilization study
DVT	Deep venous thrombosis
EMA	European Medicines Agency
ENcEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HAQ	Health Assessment Questionnaire
Hb	Hemoglobin
HCP	Healthcare professional
HMA	Heads of Medicines Agencies
Hz	Herpes zoster
ICD	International Statistical Classification of Diseases and Related Health Problems
IEC	Independent Ethics Committee
IRB	Institutional Review Board

JAK	Janus kinase
MACE	Major adverse cardiovascular event
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NHS	National Health Services
NICE	National Institute for Health and Clinical Excellence
PAC	Patient alert card
PAS	Post-authorization study
PASS	Post-authorization safety study
PE	pulmonary embolism
PRO	patient reported outcome
PT	preferred term
PVE	Pharmacovigilance and Epidemiology
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid arthritis
RABBIT	Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (Rheumatoid Arthritis: Observation of Biologic Therapy)
RCT	Randomized clinical trial
RMP	Risk management plan
SAE	Serious adverse event
SAS	Statistical Analysis Software
SmPC	Summary of product characteristics
SOP	standard operating procedure
SRQ	Swedish Rheumatology Quality Register
STAT	Signal transducer and activator of transcription
TB	Tuberculosis
TNFi	Tumor necrosis factor inhibitor
UK	United Kingdom
VAS	Visual analogue scale
VTE	Venous thromboembolism

2. RESPONSIBLE PARTIES

Table 1 Table of Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Marketing Authorization Holder	Galapagos NV Generaal De Wittelaan L11 A3 2800 Mechelen Belgium	PPD 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

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
	PPD	
RABBIT Principal Investigators	PPD	PPD
Pharmacovigilance	PPD PPD	PPD
EU&UK QPPV	PPD	PPD

3. ABSTRACT

Study Title: Non-interventional post-authorization cohort safety study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca®) use in patients with moderate to severe active rheumatoid arthritis within European registriesProtocol version: 1.0
Date: 02-Feb-2022
Author, Affiliation: PPD

Rationale and Background: Additional risk minimization measures (aRMMs) are in place to mitigate important identified and potential risks associated with the use of filgotinib. These include a healthcare professional (HCP) guide designed to increase awareness among HCPs by delivering specific information on contraindications and warnings, and a patient alert card to enhance awareness of risks and early signs and symptoms relating to specific adverse drug reactions and the best course of action to take.

To evaluate effectiveness of aRMMs and to describe filgotinib use in real-world clinical settings, a drug utilization study (DUS) will be implemented using a non-interventional follow-up (cohort) design with secondary use of data collected from 5 European rheumatoid arthritis (RA) registries: the Anti Rheumatic Treatment in Sweden (ARTIS) registry, 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 Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) registry.

Research Question and Objectives: The objectives of this study are as follows:

Objectives

- To quantify the proportion of users of filgotinib being at high risk (as defined in the risk management plan) of developing major adverse cardiovascular events (MACE), venous thromboembolism (VTE), or serious and opportunistic infections at baseline
- To quantify the proportion of filgotinib users among the very elderly (≥ 75 years) patients being initiated on filgotinib at the recommended dose of 100 mg once daily
- To quantify the proportion of filgotinib users with moderate to severe renal impairment being initiated on filgotinib at the recommended dose of 100 mg once daily
- To quantify the proportion of users of filgotinib who are being treated for active tuberculosis (TB) at the time of filgotinib treatment initiation and during follow-up (while continuing filgotinib treatment)
- To quantify the proportion of users of filgotinib who have a history of viral hepatitis at the time of filgotinib treatment initiation and during follow-up (while continuing filgotinib treatment)
- To quantify the proportion of female patients of childbearing potential who are pregnant at the time of filgotinib treatment initiation or become pregnant while continuing filgotinib treatment during follow-up
- To assess the proportion of filgotinib users receiving live, attenuated vaccines at the time of filgotinib initiation or at any time during follow-up while continuing filgotinib treatment
- To assess the proportion of filgotinib users with filgotinib discontinuation following a VTE event
- To describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring (if available), specifically:
  - To assess the proportion of filgotinib users with evidence of having performed screening for TB prior to initiation of filgotinib

○ To assess the proportion of filgotinib users with evidence of having performed lipid monitoring 12 weeks after initiation of filgotinib ○ To assess the proportion of filgotinib users with evidence of having performed the following laboratory tests prior to initiation of filgotinib: absolute neutrophil count (ANC), absolute lymphocyte count (ALC), hemoglobin (Hb) level
Study design: DUS using a non-interventional follow-up (cohort) design with secondary use of data collected from 5 European rheumatology registries (from Denmark, Germany, Spain, Sweden, and the United Kingdom). The study fulfills the criteria of a non-interventional post-authorization safety study (PASS) in accordance with the commitment to the EMA and to the MHRA.
Population: The study population will include all patients with moderate to severe active RA identified from the 5 registries who initiate treatment with filgotinib following approval in Europe, launch/commercial availability for the treatment of RA and implementation of the aRMMs in each country.
Variables: The study will include all baseline and follow-up data relevant for the specific aRMM as well as risk factors that indicate high risk of MACE, VTE or serious and opportunistic infections as available in each registry.
Data Source: The study will be conducted within 5 European rheumatology registries using their individual data sources.
Study Size: This is a descriptive study without prespecified hypotheses. All eligible patients in the 5 registries will be included, and no upper limit of the sample size will be defined.
Data Analysis: All statistical analyses will be performed by each registry. The patients' baseline and follow-up characteristics will be summarized using descriptive statistics to assess adherence to the aRMMs with respect to contraindications and monitoring, as well as the proportion of those at high risk of MACE, VTE or severe and opportunistic infections. Detailed information on the analyses will be provided in the statistical analysis plan.

Milestones: The milestones for this study are provided in the table below. An interim study report with information from all registries will be generated approximately 9 months after end of (interim) data collection, (i.e. approximately 33 months after start of data collection in the registry that last identified the first patient using filgotinib after launch/commercial availability for the treatment of RA and implementation of the aRMMs). The final study report will be submitted 12 months after end of overall data collection, (i.e. 60 months after start of data collection in the registry that last identified the first patient using filgotinib after launch/commercial availability for the treatment of RA and implementation of the aRMMs). Study reports may also be used in regulatory communications in countries outside of Europe.

Milestone	Date Planned
Registration in EU PAS register	Within 4 months after protocol approval
Start of data collection (last registry) *#	Q2 2022
End of data collection (last registry) **	Q2 2026
Interim report submission (Year 2)	Q1 2025
Final report submission (Year 4)	Q2 2027

EU = European Union; PAS = post-authorization study; Q1 = first quarter; Q2 = second quarter; Q4 = fourth quarter
* Expected date of the last registry to include the first patient initiating filgotinib
** Expected date of the last registry to include the first patient initiating filgotinib + 48 months
# 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 Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

The milestones for the study are presented below in Table 2. Data collection and study report milestones are based on assumptions of commercial availability of filgotinib. The time required to analyze and submit the reports, whilst estimated to be 6 months, is dependent on the timing of the required data linkages.

Each registry will be deemed to have started data collection as from the date of the first patient initiating filgotinib. Milestones will therefore use this date for each registry as the reference point.

Each registry will generate an interim study report after 24 months of data collection following the study start date for that registry; the interim report will take approximately 9 months. A full analysis will be performed after 48 months of data collection; the full report and analyses will take approximately 12 months. Thus, the consolidated reports will be created once the last registry has provided its results. It is noted that ARTIS and DANBIO may require additional time for linkage data to be available.

If any registries were unable to provide the agreed reports (e.g. due to unavailability of filgotinib-exposed patients, local regulatory changes, etc.), then 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(ies).

The overall study timeframe will therefore account for the timing of the start of the study for each registry, the data collection periods and the subsequent time required to perform each analysis (data management, linkage, statistical analysis and report writing) and the creation and submission of the consolidated interim and final reports.

Table 2 Milestones

Milestone	Date Planned
Registration in EU PAS register	Within 4 months after protocol approval
Start of data collection (last registry) [a,c]	Q2 2022
End of data collection [b]	Q2 2026
Interim report submission (Year 2)	Q1 2025
Final report submission (Year 4)	Q2 2027

EU = European Union; PAS = post-authorization study; Q1 = first quarter; Q2 = second quarter; Q4 = fourth quarter

a. * Expected date of the last registry to include the first patient initiating filgotinib

b. ** Expected date of the last registry to include the first patient initiating filgotinib + 48 months

c. # Patients may be entered into the registry prior to protocol finalization as the data fields are fixed by the registry

6. 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 (CVD) (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 1 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. For this reason, a post-authorization safety study (PASS) assessing the long-term safety of filgotinib is planned (protocol number GS-EU-417-9047). Furthermore, additional risk minimization measures (aRMMs) are in place to mitigate important identified and potential risks associated with the use of filgotinib. These include a healthcare professional (HCP) guide designed to increase awareness among HCPs by delivering specific information on contraindications and warnings and a patient alert card (PAC) to enhance awareness of risks and early signs and symptoms relating to specific adverse drug reactions (ADRs) and the best course of action to take. The purpose of this PASS, therefore, is to assess the effectiveness of these aRMMs and to characterize the risk-profile of patients with moderate to severe active RA who initiate filgotinib within the same 5 European RA registries used for GS-EU-417-9047, i.e. the "Anti-Rheumatic Treatment in Sweden" (ARTIS) registry, 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 Biologika-Therapie" (RABBIT).

This PASS is being conducted by the MAH as a Category 3 commitment to the European Medicines Agency (EMA) and to the Medicines and Healthcare products Regulatory Agency (MHRA).

6.1. Safety Outcomes of Concern: Rationale and Definition

With the aim of reducing potential risks associated with filgotinib, the HCP guide will address:

- Serious and opportunistic infections
- Herpes zoster
- Embryolethality and teratogenicity
- Impaired spermatogenesis
- Venous thromboembolism (VTE)
- Major adverse cardiovascular events (MACE)
- Use in the very elderly (≥75 years)

The summary of product characteristics (SmPC) states that patients with active tuberculosis (TB), active serious infections, or those women who are pregnant are contraindicated for treatment with filgotinib. Furthermore, patients aged 75 and older should have a starting daily dose of 100 mg as should patients with moderate or severe renal impairment (stages 3 or 4; creatinine clearance [CrCl] 15 to <60 mL/min). Screening activities include screening for TB and viral hepatitis as well as blood tests including neutrophil and lymphocyte counts, hemoglobin and lipid parameters. Further to this, the SmPC includes warnings that MACE, VTE and serious and

opportunistic infections are important safety concerns; infections are considered the main risk of immunomodulatory therapy. The following definitions are applied for these outcomes:

- MACE: Includes fatal and nonfatal CVD events. CVD comprises coronary heart disease (angina, myocardial infarction), congestive heart failure, cerebrovascular disease and peripheral artery disease.
- VTE: Includes deep venous thrombosis (DVT) and pulmonary embolism (PE).
- Serious and opportunistic infections: Opportunistic infections occur among people with weakened immune systems; such infections may be mild in people with healthy immune response but can be more serious among patients who are using immune-modulatory therapy. The overall rate of treatment-emergent serious adverse events (SAEs) at 200 mg (integrated safety summary) for serious infections was around 3.0%, among which the rate for pneumonia was 0.8%; opportunistic infections were 0.2%. The list of preferred terms in MedDRA currently comprises 192 terms under "Serious and Opportunistic infections".

The risk management plan (RMP) classifies MACE and VTE as "*important potential risks*," while serious and opportunistic infections (and herpes zoster) are considered "*important identified risks*." TB and other opportunistic infections are more frequent in patients with RA; the reasons are likely multifactorial although increased risk has been identified with the use of glucocorticoids and other biologic DMARDs. To date there have been no safety signals arising from the filgotinib clinical development program for MACE, however the potential role of hyperlipidemia on the risk of MACE warrants continued assessment. Regarding VTEs, there was no imbalance in the occurrence of these events from the clinical development program however the RMP states "*With RA patients and patients with ulcerative colitis having a higher risk of VTEs, and VTEs having been associated with some JAK inhibitors, venous thromboembolism (DVT/PE) has been classified as an important potential risk*".

Pregnancy is a contraindication for filgotinib as teratogenicity was observed in animals. Thus, women of childbearing potential must be encouraged to use effective contraception during treatment and for at least 1 week after stopping filgotinib treatment.

Serious and opportunistic infections (including herpes zoster and TB) are higher in patients with RA and is increased with the use of prednisone and some biological DMARDs. Thus, there may be increased risk of such infections among patients with poor immune systems or due to the use of immunosuppressant medication.

6.2. Physician Adherence

Physician adherence implies compliance with the SmPC and the HCP Guide. Firstly, this includes the avoidance of administering filgotinib to contraindicated patients: those with active TB, or active serious infection or being pregnant at initiation of treatment and while continuing filgotinib treatment. Secondly, the physician should undertake appropriate screening prior to prescribing filgotinib: screening for TB and viral hepatitis. Furthermore, information on the use of live, attenuated vaccines during, or immediately prior to, filgotinib treatment, and the provision of guidance to women of childbearing potential will be evaluated. Lastly, prescribed doses should be in line with the recommendations. Thus, this will be evaluated for patients aged

≥ 75 or patients with moderate to severe renal impairment whose starting dose should be 100 mg daily.

In terms of adherence during filgotinib use, several endpoints should be monitored:

- Given that pregnancy is a contraindication for filgotinib, should a woman become pregnant, filgotinib must be discontinued.
- If a VTE occurs ("clinical features of DVT/PE"), filgotinib should be discontinued and the patients be evaluated.
- Patients should be monitored for the development of signs and symptoms of TB.
- Lipid parameters should be monitored at 12 weeks after initiation of treatment.
- Live attenuated vaccines should be avoided during filgotinib treatment.

6.3. Registries

Several disease-based prospective rheumatology registries have been established in Europe to evaluate the safety profiles of new biologics, biosimilars or other advanced targeted therapies (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), MACE (Ljung et al., 2014; Low et al., 2017; Meissner et al., 2017), risk of VTE (Davies et al., 2011; Holmqvist et al., 2012), and mortality (Listing et al., 2015; Simard et al., 2012)). They have been used extensively to address post-authorization safety requirements and hence, such registries are suitable for the aims of this aRMMs effectiveness evaluation, hereafter referred to as aRMMs PASS. ARTIS, BIOBADASER, BSRBR-RA, DANBIO, and RABBIT are established rheumatology registries in Europe; details are given in Section 8.2 and Section 8.4.

6.4. Purpose

Given the previously described purpose of this PASS, this study will be implemented using data from the 5 European registries mentioned above, i.e. Sweden's ARTIS, BIOBADASER from Spain, BSRBR-RA from the United Kingdom (UK), DANBIO from Denmark, and RABBIT from Germany. This study will report whether patients already have experienced the above outcomes at baseline (i.e. at the time of the first identification of filgotinib exposure in the registry) or will experience them with continuous filgotinib treatment during follow-up, and will also ascertain which patients, who start filgotinib, may be at high risk of these outcomes due to their risk-profile at initiation of filgotinib. Thus, this PASS will assess the HCP adherence (i.e. avoidance of contraindicated populations and use of screening prior to administration of filgotinib) and will also estimate those patients at high risk of the outcomes of concern (MACE, VTE and serious and opportunistic infection).

7. RESEARCH QUESTION AND OBJECTIVES

The objectives of this study are as follows:

- To quantify the proportion of users of filgotinib being at high risk (as defined in the RMP) of developing MACE, VTE, or serious and opportunistic infections at baseline
- To quantify the proportion of filgotinib users among the very elderly (≥75 years) patients being initiated on filgotinib at the recommended dose of 100 mg once daily
- To quantify the proportion of filgotinib users with moderate to severe renal impairment being initiated on filgotinib at the recommended dose of 100 mg once daily
- To quantify the proportion of users of filgotinib who are being treated for active TB at the time of filgotinib treatment initiation and during follow-up (while continuing filgotinib treatment)
- To quantify the proportion of users of filgotinib who have a history of viral hepatitis at the time of filgotinib treatment initiation and during follow-up (while continuing filgotinib treatment)
- To quantify the proportion of female patients of childbearing potential who are pregnant at the time of filgotinib treatment initiation or become pregnant while continuing filgotinib treatment during follow-up
- To assess the proportion of filgotinib users receiving live, attenuated vaccines at the time of filgotinib initiation or at any time during follow-up while continuing filgotinib treatment
- To assess the proportion of filgotinib users with filgotinib discontinuation following a VTE event
- To describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring (if available), specifically:
  - To assess the proportion of filgotinib users with evidence of having performed screening for TB prior to initiation of filgotinib
  - To assess the proportion of filgotinib users with evidence of having performed lipid monitoring 12 weeks after initiation of filgotinib
- To assess the proportion of filgotinib users with evidence of having performed the following laboratory tests prior to initiation of filgotinib: absolute neutrophil count (ANC), absolute lymphocyte count (ALC), hemoglobin (Hb) level

8. RESEARCH METHODS

8.1. Study Design

This is a drug utilization study (DUS) using a non-interventional follow-up (cohort) design with secondary use of data collected from 5 European rheumatology registries (from Denmark, Germany, Spain, Sweden, and the UK). The study fulfills the criteria of a non-interventional PASS.

The study population will include all patients enrolled in the 5 registries with moderate to severe active RA who initiate treatment with filgotinib following approval in Europe,

launch/commercial availability for the treatment of RA and implementation of the aRMMs in each country.

The observational study period in each registry will start with the first patient identified with filgotinib use after launch/commercial availability for the treatment of RA and implementation of the aRMMs in each country and will end 48 months after identification of the first filgotinib patient in each registry.

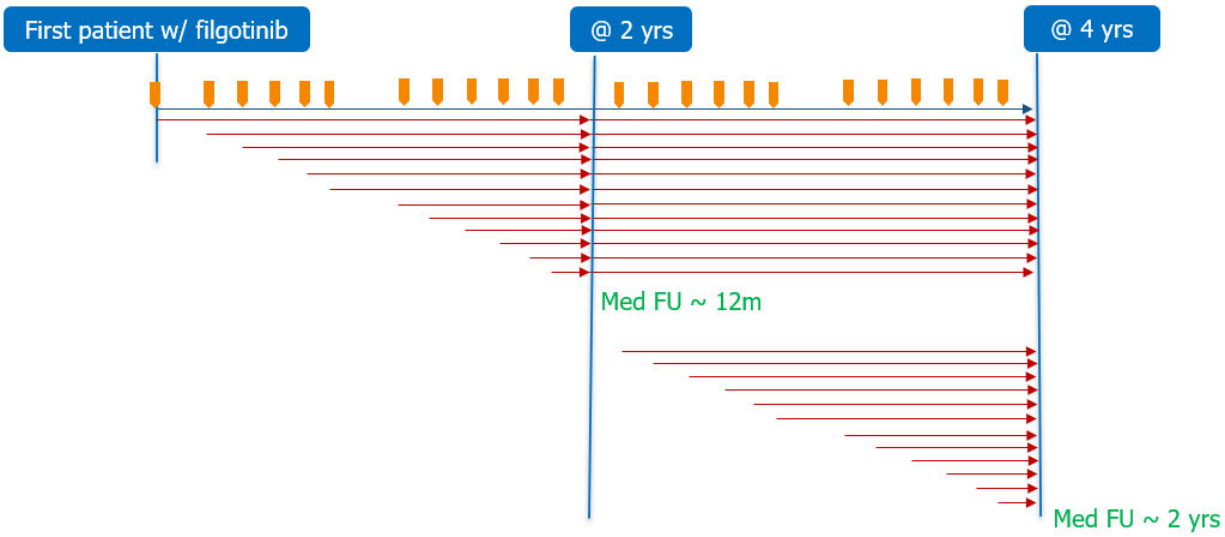


Figure 1 Summary Schematic of the aRMM PASS

The above figure depicts the PASS execution for each registry from which 2 reports will be generated, an interim and a final study report. Therefore, given that the registries will start at differing times, the time to complete the data collection for the overall study will last longer than 48 months. The figure also indicates that a median of 12 months follow-up and 24 months follow-up will be collected at 24 and at 48 months, respectively. This is, however, a maximum estimation as the uptake of filgotinib is unlikely to be uniform, with greater uptake towards the latter part of the study period.

The time required to produce the reports will vary due to data delays associated with the process of data linkage and thus may not be ready at 9 or 12 months, respectively, from the end of the observational periods.

8.2. Setting

8.2.1. ARTIS (Sweden)

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 (S. 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 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 registers is possible (Ludvigsson et al., 2009). The registers are maintained by governmental bodies (the main registers used in this project 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.

Use of biologic and other targeted RA treatments in Sweden has never been subject to any formal approvals (except for a period during 2002-2003, 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

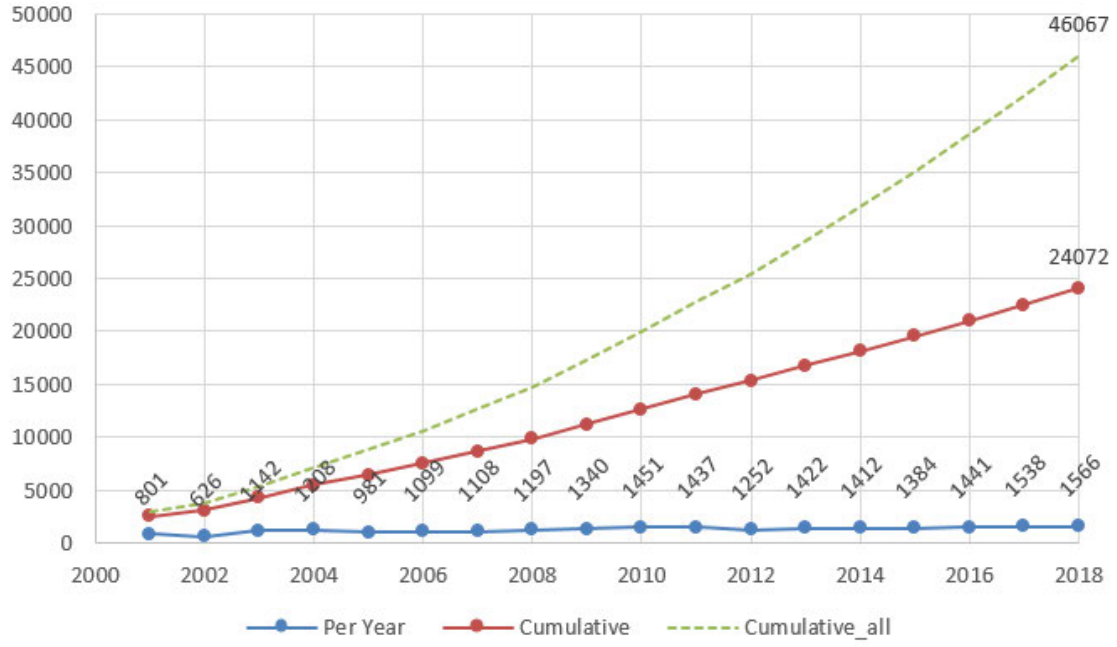
The Swedish Rheumatology Quality Register (SRQ) was started in 1995 by the Swedish Society of Rheumatology to improve the healthcare and treatment for patients with RA (J. K. Eriksson et al., 2014). SRQ followed on regional register initiatives to enable a national real-world documentation of many different aspects of RA and developed over time into a harmonized national register. 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 register 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 40,000 patients (65% women) and more than 80,000 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 2 depicts the accumulated number of patients, and Figure 3 shows the total number of treatment episodes and their distribution across specific drugs.



Dashed line, across all indications; bold lines, RA.

Figure 2 Accumulated Number of First Ever Biologic Initiations Registered in the Swedish Rheumatology Quality Register (SRQ)

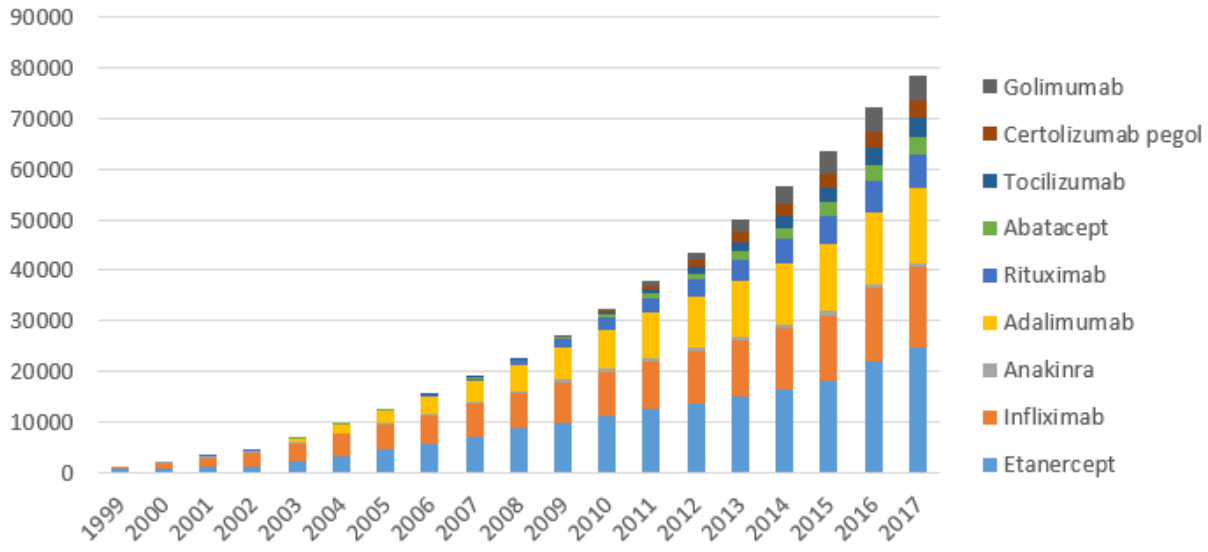


Figure 3 Cumulative Number of Treatment Initiations in the Swedish Follow-up on Biologics Treatment Among Patients with Rheumatic Diseases

ARTIS is designed to assist in signal detection (through facilitated reporting and contextualization of ADRs), signal evaluation (through register 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).

8.2.2. BIOBADASER (Spain)

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 (TNFi) agents and the reactivation of latent TB 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).

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 register, 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

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 non-experimental 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

8.2.3. BSRBR-RA (UK)

BSRBR-RA is a registry-based on an ongoing prospective non-interventional cohort study design 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 7-8 years, the main focus was on the study of the safety profile of the first 3 tumor TNFi agents (i.e. adalimumab, etanercept, and infliximab) as a class and as individual therapies. With the exception of the risk of developing TB, 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 were 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.

The British Society for Rheumatology (BSR) 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.

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 (GPP) for Post-Authorisation Safety Studies, EMA and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENcEPP) Guide on Methodological Standards in Pharmacoepidemiology.

8.2.4. DANBIO (Denmark)

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).

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.

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; Schmidt et al., 2015).

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. A nationwide biobank (i.e. blood and synovial fluid) associated with DANBIO was established in 2015 (Hetland, 2011).

8.2.5. RABBIT (Germany)

The German biologics registry RABBIT is an independent academia driven long-term observational cohort study of patients with RA. RABBIT is being conducted by Deutsches Rheuma Forschungszentrum Berlin (German Rheumatism Research Center [DRFZ]) with joint pharmaceutical industry funding. 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 SAEs in order to assess the overall safety profile. Specific emphasis will be put on the “events of interest”
- 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, health-related quality of life and functional status.

– To describe health care consumption and work disability with different drugs.

RA treating physicians 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 registered in RABBIT should have: 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 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.

8.2.6. Index Date, Follow-up, Inclusion and Exclusion Criteria

For all analyses, the index date in each registry will be the date a patient starts filgotinib treatment (i.e. the date of first identification of filgotinib exposure in the registry) on or after launch/commercial availability for the treatment of moderate to severe RA and implementation of the aRMMs in each country. The patient follow-up time is defined as the time from the filgotinib index date until the earliest of treatment discontinuation, study withdrawal (withdrawn from the registry, death or loss to follow-up) or end of study.

The observational (study) period for each registry starts at the index date of the first patient starting filgotinib treatment in the registry (i.e. start of data collection). End of the study period will be at 48 months after the start of data collection in the registry (i.e. end of data collection).

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; patients must meet all eligibility criteria.

There are no restrictions to patient inclusion in terms of either historical data or minimum amount of follow-up. Furthermore, patients can be included if they have previously used filgotinib, in which case the patient will have 2 or more treatment lines and therefore 2 or more index dates.

8.2.7. Inclusion Criteria

All patients initiating filgotinib in the observational period to treat moderate to severe RA and who comply with the register's requirements for inclusion (including patient consent) will be included. Thus, there is no limit in terms of age, although only adults (≥18) are included in ARTIS, or in terms of prior use of filgotinib; initiation is therefore defined as either no prior use or prior use that was discontinued (thus, patients who are non-naïve to filgotinib can be included).

1. Initiation of filgotinib treatment in the observational periods as captured in ARTIS.

2. RA diagnosis by a consulting rheumatologist.

8.2.8. Exclusion Criteria

No exclusion criteria are considered.

8.3. Variables

8.3.1. Baseline Variables

Baseline variables are collected at index date. These variables reflect the patient's demographics and status at the initiation of filgotinib treatment including relevant medical history at or prior to the index date. Age (or date of birth), sex, disease duration and DAS28 are recorded at baseline for all registries.

Risk factors for MACE, VTE, and Serious and Opportunistic Infections

Variables will be collected at baseline to define the risk of each of the 3 outcomes of concern: MACE, VTE, and serious and opportunistic infections (see definitions in Section 6.1 and Annex 4).

The set of risk factor definitions were derived utilizing broader representation than that solely included in the RMP and then checked against data availability in each registry. The set of risk factors are provided in tables in each of the registry-specific sections, which reflect the availability of variables for each registry.

For MACE, the UK's Q-Risk score was used as a guide (Hippisley-Cox et al., 2008). We note that RA is a risk factor for MACE/CVD implying that the indicated patient population are at higher risk than the general population (after adjusting for age and sex). RA is available in all registries as a risk factor, as all patients have RA.

For VTE, the Jyseleca RMP mentions the following risk factors for VTE: "*prior history of VTE, advanced age, hormone replacement treatment, obesity, smoking, cancer or immobilization*". These risk factors are supplemented by considering the Caprini Score (Bahl et al., 2010), a perioperative assessment tool for new VTE. The Caprini Score highlighted the importance of a lack of mobility and hospitalization have on VTE risk.

For serious and opportunistic infections, the RMP highlighted that patients with RA were at increased risk and that the "*The reasons are multifactorial, including a poorly functioning immune system and concomitant use of immunosuppressant medications such as glucocorticoids*". The use of immunomodulators implies that patients initiating filgotinib are already at increased levels of risk. The set of risk factors for infection were supplemented by those indicated by the Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) Risk Score for serious infections (Zink et al., 2014).

The availability of the variables in each registry that define the risk of MACE, VTE and serious and opportunistic infections is defined in the following sections. Other baseline variables (patient characteristics) captured at baseline are also provided in these sections.

8.3.1.1. ARTIS

Patient Baseline Characteristics

Baseline variables will include the following:

- Age (at baseline)
- Sex
- Renal impairment
  - Stage (if available)
- Date of initiation of filgotinib
- Initial dose of filgotinib
- First ever administration of filgotinib: y/n
- Previous RA treatment immediately prior to initiation of filgotinib
- Date of diagnosis of RA (year; approximate if greater than 10 years earlier)
- Current severity of RA
  - Disease Activity Score (DAS):
    - DAS for 28 joint count (DAS28)
    - DAS28 type: Erythrocyte Sedimentation Rate (ESR); C-reactive protein (CRP)
    - CRP value
    - ESR value
  - Health Assessment Questionnaire (HAQ) score
  - Visual analogue scale (VAS; patient assessment of disease)
  - RA type (seropositive, seronegative)
  - Date of assessment

Risk Factors for MACE, VTE, and Serious and Opportunistic Infections

As previously described, each registry was assessed for the availability of the set of potential risk factors for the 3 endpoints of concern. In ARTIS there are no measures of obesity or immobility, both risk factors for VTE, although HAQ could be used as a proxy.

Table 3 Risk Factors for MACE, VTE and Serious and Opportunistic Infections as Available in ARTIS

	MACE	VTE	Serious and Opportunistic Infections
History of cardiovascular disease	Yes		
History of VTE		Yes	
Previous serious infection			Yes
Age	Yes	Yes	Yes
Sex	Yes		
Diabetes type 1	Yes		Yes
Diabetes type 2	Yes		Yes
Atrial fibrillation	Yes		
Chronic kidney disease	Yes		Yes
Smoking	Yes	Yes	
Family history CVD	Yes		
Use of treatment: Hyperlipidemia (Dx unavailable)	Yes		
Use of treatment: Hypertension (Dx unavailable)	Yes		
Cancer diagnosis (date)	Yes	Yes	Yes
Known thrombophilic condition		Yes	
Reduced mobility / Hospitalization (date, type, length of stay)		Yes	
Trauma and/or surgery		Yes	

	MACE	VTE	Serious and Opportunistic Infections
Ongoing hormonal replacement therapy		Yes	
Heart and/or respiratory failure		Yes	
Acute myocardial infarction or ischemic strokes		Yes	
Chronic lung disease			Yes
Glucocorticoid			Yes
TNFi			Yes
Other immunosuppressant/modifying treatment			Yes

CVD = cardiovascular disease; Dx = diagnosis; MACE = major adverse cardiovascular event; TNFi = tumor necrosis factor inhibitor; VTE = venous thromboembolism

Physician Adherence

In accordance with the RMP, SmPC and the description provided in Section 6.2, the following variables will be used to describe the adherence of the prescribing physician with respect to the Guide for HCP:

- Diagnosis of TB: yes/no
  - Date of diagnosis
- Diagnosis of herpes zoster: yes/no
  - Date of diagnosis
- Diagnosis of viral hepatitis: yes/no
  - Date of diagnosis
- Patient is currently pregnant (defined as greater than 25 weeks): yes/no
- Date of most recent full term pregnancy (for women aged <50 years old)
- Recent diagnosis of serious and opportunistic infection: yes/no
  - Type of infection
  - Date of diagnosis

Dose and age are already variables for this study and thus the use of 100 mg in patients aged ≥75 years old and in patients with chronic kidney disease can be addressed.

Concomitant Medication

The SmPC includes a warning that certain concomitant treatments should be avoided. Specifically, combination of filgotinib with other potent immunosuppressants such as azathioprine, ciclosporin, tacrolimus, biologic DMARDs, or other JAK inhibitors is not

recommended as a risk of additive immunosuppression cannot be excluded. For this reason, concomitant use will be recorded; this will not include any previous medication that is discontinued once filgotinib is first prescribed. Thus, this will capture those immunosuppressants that are prescribed to start with filgotinib or that are ongoing.

– Concomitant use of other immunosuppressant:
  - Type, name, and dose (incomplete)
  - Dates of dispensing

8.3.1.2. BIOBADASER

Baseline characteristics captured by BIOBADASER are collected from the recruiting clinician or directly from each patient enrolled in the register using an electronic standardized form. The variables to be captured by the register are summarized in the following section.

Patient Baseline Characteristics

Baseline variables will include the following:

– Age (at baseline)
– Sex
– Renal impairment
– Date of initiation of filgotinib
– Initial dose of filgotinib
– First ever administration of filgotinib: y/n
– Previous RA treatment immediately prior to initiation of filgotinib
– Date of diagnosis of RA (year)
– Current severity of RA
  - Disease Activity Score (DAS):
    - DAS for 28 joint count (DAS28)
    - DAS28 type: ESR; CRP
    - CRP value
    - ESR value
  - VAS (patient assessment of disease)
  - RA type (seropositive, seronegative)
  - Date of assessment

Risk Factors for MACE, VTE, and Serious and Opportunistic Infections

As previously described, each registry was assessed for the availability of the set of potential risk factors for the 3 endpoints of concern.

Table 4 Risk Factors for MACE, VTE and Serious and Opportunistic Infections as Available in BIOBADASER

	MACE	VTE	Serious and Opportunistic Infections
History of CVD	Yes		
History of VTE		Yes	
Previous serious infection			Yes
Age	Yes	Yes	Yes
Sex	Yes		
Diabetes	Yes		Yes
Chronic kidney disease (stages 4, 5)	Yes		Yes
Smoking	Yes	Yes	
Hyperlipidemia	Yes		
Hypertension	Yes		
Active cancer & history of cancer		Yes	
Recent hospitalization		Yes	
Recent surgery		Yes	
Known thrombophilic condition		Yes	
Ongoing hormonal replacement therapy		Yes	
Heart and/or respiratory failure		Yes	
Acute myocardial infarction or ischemic strokes		Yes	
Obesity or BMI		Yes	
Acute infection and/or rheumatologic disorder		Yes	
Chronic lung disease			Yes

	MACE	VTE	Serious and Opportunistic Infections
Prior DMARD treatment failure			Yes
Glucocorticoid			Yes
TNFi			Yes

BMI = body mass index; CVD = cardiovascular disease; DMARD = disease-modifying antirheumatic drug; MACE = major adverse cardiovascular event; TNFi = tumor necrosis factor inhibitor; VTE = venous thromboembolism

Physician Adherence

In accordance with the RMP, SmPC and the description provided in Section 6.2, the following variables will be used to describe the adherence of the prescribing physician with respect to the Guide for HCP.

- Diagnosis of TB: yes/no
  - Date of diagnosis
- Diagnosis of herpes zoster: yes/no
  - Date of diagnosis
- Diagnosis of viral hepatitis: yes/no
  - Date of diagnosis
- Patient is currently pregnant: yes/no
  - Weeks pregnant
- Date of most recent full term pregnancy (for women aged < 50 years old)
- The patient is suffering from a serious and opportunistic infection (as defined by MedDRA): yes/no
  - Infection type
  - Date of diagnosis

Dose and age are already variables for this study and thus the use of 100 mg in patients aged ≥75 years old and in patients with chronic kidney disease can be addressed.

- Screening:
  - TB
  - Date of screening
  - Result of screening test

Concomitant Medication

- Concomitant use of other immunosuppressant:
  - Type, name, and dose (where recorded)

Additional Variables: Laboratory and Counselling

BIOBADASER is the only registry that can supplement their data through additional data collection screens based on clinical practice. The additional variables are summarized below.

Table 5 Additional Variables in BIOBADASER

Variable			
ANC (neutrophils)	Value	units	Date
ALC (lymphocytes)	Value	units	Date
Hb	Value	units	Date
HDL	Value	units	Date
LDL	Value	units	Date
Total cholesterol	Value	units	Date
triglycerides	Value	units	Date
HDL:LDL	Value	units	Date
Advice given on contraceptive use	y/n		
Advice given on spermatogenesis	y/n		
Advice given on breast feeding	y/n		

ALC = absolute lymphocyte count; ANC = absolute neutrophil count; Hb = hemoglobin; HDL = high density lipoprotein; LDL = low density lipoprotein

8.3.1.3. BSRBR-RA

Patient Baseline Characteristics

Baseline variables will include the following:

- Age (at baseline)
- Sex
- Renal impairment
- Date of initiation of filgotinib
- Initial dose of filgotinib
- First ever administration of filgotinib: y/n
- Previous RA treatment immediately prior to initiation of filgotinib

- Date of diagnosis of RA (year)
- Current severity of RA
  - DAS:
    - DAS for 28 joint count (DAS28)
    - DAS28 type: ESR; CRP
    - CRP value
    - ESR value
  - HAQ score
  - VAS (patient assessment of disease)
  - RA type (seropositive, seronegative)
  - Date of assessment

Risk Factors for MACE, VTE, and Serious and Opportunistic Infections

A set of variables will be collected at baseline to define the risk of each of the 3 outcomes of concern: MACE, VTE, and serious and opportunistic infections (see definitions in Section 6.1 and Annex 4).

As previously described, each registry was assessed for the availability of the set of potential risk factors for the 3 endpoints of concern.

Table 6 Risk Factors for MACE, VTE and Serious and Opportunistic Infections as Available in BSRBR-RA

	MACE	VTE	Serious and Opportunistic Infections
History of CVD	Yes		
History of VTE		Yes	
Previous serious infection (partial availability)			Yes
Age	Yes	Yes	Yes
Sex	Yes		
Diabetes type 1	Yes		Yes
Diabetes type 2	Yes		Yes
Atrial fibrillation	Yes		
Chronic kidney disease (stages 4,5)	Yes		Yes
Smoking	Yes	Yes	

	MACE	VTE	Serious and Opportunistic Infections
Hyperlipidemia	Yes		
Hypertension	Yes		
Cancer and date of diagnosis		Yes	
Ongoing hormonal replacement therapy		Yes	
Acute myocardial infarction or ischemic strokes		Yes	
Obesity or BMI		Yes	
Chronic lung disease			Yes
Glucocorticoid			Yes
TNFi			Yes
Other immunosuppressant/modifying treatment			Yes

BMI = body mass index; CVD = cardiovascular disease; MACE = major adverse cardiovascular event; TNFi = tumor necrosis factor inhibitor; VTE = venous thromboembolism

Physician Adherence

In accordance with the RMP, SmPC and the description provided in Section 6.2, the following variables will be used to describe the adherence of the prescribing physician with respect to the Guide for HCP.

- Diagnosis of active TB: yes/no
  - Date of diagnosis
- Diagnosis of herpes zoster: yes/no
  - Date of diagnosis
- Diagnosis of viral hepatitis: yes/no
  - Date of diagnosis
- Previous opportunistic infection: yes/no
  - Date of diagnosis: yes/no
- Pregnancy: yes/no

Dose and age are already variables for this study and thus the use of 100 mg in patients aged ≥75 years old and in patients with chronic kidney disease can be addressed.

- Screening:

- TB
- Date of screening
- Result of screening test

– Record of recent administration of herpes zoster (live attenuated) vaccine:
  - Date

Concomitant Medication

– Concomitant use of other immunosuppressant:
  - Type, name, dates and dose

8.3.1.4. DANBIO

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, and other disease related variables (including previous DMARD treatments, anti-cyclic citrullinated peptide, and immunoglobulin M rheumatoid factor status, disease activity measures), socio demographic factors (age, sex), and health behavioral factors (including tobacco use) are registered.

The variables for the study will be collected at baseline; this is the date of each patient's first prescription/administration of filgotinib in the observational period. These variables reflect the patient's status at baseline (initiation of filgotinib) or the medical history prior to and including the baseline date. The variables to be captured by the register are summarized in the following section.

Patient Baseline Characteristics

Baseline variables will include the following:

– Age (at baseline)
– Sex
– Renal impairment
  - Current stage (1 to 5)
– Date of initiation of filgotinib
– Initial dose of filgotinib
– First ever administration of filgotinib: y/n
– Previous RA treatment immediately prior to initiation of filgotinib
– Date of diagnosis of RA (year)
– Current severity of RA
  - DAS28 CRP
  - HAQ score
  - VAS (patient assessment of disease)
  - RA type (seropositive, seronegative)

- Date of assessment

Risk Factors for MACE, VTE, and Serious and Opportunistic Infections

As previously described, each registry was assessed for the availability of the set of potential risk factors for the 3 endpoints of concern. With regards to serious and opportunistic infections, it is worth noting that DANBIO developed a risk score for infection (Krabbe et al., 2021). The risk factors considered are age, previous serious infection, pulmonary disease, diabetes and myocardial infarction and glucocorticoid use within the last year.

Table 7 Risk Factors for MACE, VTE and Serious and Opportunistic Infections as Available in DANBIO

	MACE	VTE	Serious and Opportunistic Infections
History of CVD	Yes		Yes
History of VTE		Yes	
Previous serious infection			Yes
Age	Yes	Yes	Yes
Sex	Yes		
Diabetes type 1	Yes		Yes
Diabetes type 2	Yes		Yes
Atrial fibrillation	Yes		
Smoking	Yes	Yes	
Hyperlipidemia	Yes		
Hypertension	Yes		
Active cancer & history of cancer		Yes	
Known thrombophilic condition		Yes	
Reduced mobility / Hospitalization (date, type, length of stay)		Yes	
Trauma and/or surgery		Yes	

	MACE	VTE	Serious and Opportunistic Infections
Ongoing hormonal replacement therapy		Yes	
Heart and/or respiratory failure		Yes	
Acute myocardial infarction or ischemic strokes		Yes	
Obesity or BMI		Yes	
Acute infection and/or rheumatologic disorder		Yes	
Chronic lung disease			Yes
Prior DMARD treatment failure			Yes
Glucocorticoid			Yes
TNFi			Yes
Other immunosuppressant/modifying treatment			Yes

BMI = body mass index; CVD = cardiovascular disease; DMARD = disease-modifying antirheumatic drug; MACE = major adverse cardiovascular event; TNFi = tumor necrosis factor inhibitor; VTE = venous thromboembolism

Physician Adherence

In accordance with the RMP, SmPC and the description provided in Section 6.2, the following variables will be used to describe the adherence of the prescribing physician with respect to the Guide for HCP.

- Diagnosis of TB: yes/no
  - Date of diagnosis
- Diagnosis of herpes zoster: yes/no
  - Date of diagnosis
- Diagnosis of viral hepatitis: yes/no
  - Date of diagnosis
- Patient is currently pregnant: yes/no
  - Weeks pregnant
- Date of most recent full term pregnancy (for women aged <50 years old)
- The patient is suffering from a serious and opportunistic infection (as defined by MedDRA): yes/no
  - Date of diagnosis

Dose and age are already variables for this study and thus the use of 100 mg in patients aged ≥75 years old and in patients with chronic kidney disease can be addressed.

Concomitant Medication

- Concomitant use of other immunosuppressant (csDMARDs, prednisolone):
  - Type, name, and dose
  - Dates of prescriptions

8.3.1.5. RABBIT

This study will make secondary use of prospectively collected existing data in the RABBIT registry. Baseline data captured in RABBIT are collected by the recruiting physicians using a standardized form.

Patient Baseline Characteristics

Baseline variables will include the following:

- Age (at baseline)
- Sex
- Renal impairment
- Date of initiation of filgotinib
- Initial dose of filgotinib
- First ever administration of filgotinib: y/n
- Previous RA treatment immediately prior to initiation of filgotinib
- Date of diagnosis of RA (year)
- Current severity of RA
  - Disease Activity Score (DAS):
  - DAS for 28 joint count (DAS28)
  - DAS28 type: ESR; CRP
  - CRP value
  - ESR value
  - HAQ (from FFbH Hannover) score
  - RA type (seropositive, seronegative)
  - Date of assessment

Risk Factors for MACE, VTE, and Serious and Opportunistic Infections

As previously described, each registry was assessed for the availability of the set of potential risk factors for the 3 endpoints of concern.

Table 8 Risk Factors for MACE, VTE and Serious and Opportunistic Infections as Available in RABBIT

	MACE	VTE	Serious and Opportunistic Infections
History of CVD	Yes		
Age	Yes	Yes	Yes
Sex	Yes		
Diabetes	Yes		Yes
Chronic kidney disease	Yes		Yes
Smoking	Yes	Yes	
Hyperlipidemia	Yes		
Hypertension	Yes		
Active cancer		Yes	
Hospitalization (date, type, length of stay)		Yes	
Surgery		Yes	
Heart and/or respiratory failure		Yes	
Acute myocardial infarction or ischemic strokes		Yes	
Obesity or BMI		Yes	
Acute infection and/or rheumatologic disorder		Yes	
Chronic lung disease			Yes
Prior DMARD treatment failure			Yes
Glucocorticoid			Yes
TNFi			Yes
Other immunosuppressant/modifying treatment			Yes

BMI = body mass index; CVD = cardiovascular disease; DMARD = disease-modifying antirheumatic drug; ; MACE = major adverse cardiovascular event; TNFi = tumor necrosis factor inhibitor; VTE = venous thromboembolism

Physician Adherence

In accordance with the RMP, SmPC and the description provided in Section 6.2, the following variables will be used to describe the adherence of the prescribing physician with respect to the Guide for HCP.

- Diagnosis of TB: yes/no
  - Date of diagnosis
- Diagnosis of herpes zoster: yes/no
  - Date of diagnosis
- Diagnosis of viral hepatitis: yes/no
  - Date of diagnosis
- Patient is currently pregnant: yes/no
  - Weeks pregnant

Dose and age are already variables for this study and thus the use of 100 mg in patients aged ≥75 years old and in patients with chronic kidney disease can be addressed.

- Record of recent administration of vaccines:
  - Date and type of vaccine (live attenuated; inactivated, mRNA; subunit type; toxoid, viral vector)
- Screening (at baseline and every 2.5 years):
  - TB
  - Viral hepatitis

Concomitant Medication

- Concomitant use of other immunosuppressant:
  - Type, name, date and dose

8.3.2. Variables to be Collected During Patient Follow-up

The variables to be collected during the follow-up which will describe endpoints (see Section 6.2) related to aRMMs adherence are provided in the following table. These therefore include pregnancy, use of vaccines and lipid monitoring. Monitoring of TB following the initial screening for latent disease is not included: firstly, testing is not required and; secondly, evaluating whether clinicians routinely check for signs and symptoms is not be feasible via registry data.

As well as the occurrence of the variables, appropriate dates will be collected. Furthermore, the patients' index dates, end of treatment and end of follow-up dates will be used to estimate the exposure time.

Table 9 Availability of Endpoints to Assess Adherence by Registry During Patient Follow-up

Follow-up Variable	ARTIS	BIOBADASER	BSRBR-RA	DANBIO	RABBIT
Pregnancy	Yes	Yes	Yes	Yes	Yes
Dx of incident TB	Yes	Yes	Yes	Yes	Yes
Viral hepatitis	Yes	Yes	Yes	Yes (only history)	Yes
Administration of live attenuated vaccine	No	Yes	Yes (HZ only)	No	Yes
Lipid monitoring (approx.. 12 weeks after initiation of filgotinib)	No	Yes	No	No	No

Dx = diagnosis, HZ = herpes zoster, TB = tuberculosis

In addition to the above variables, the occurrence of a VTE event whilst the patient is using filgotinib will be identified and specifically the subsequent treatment pattern occurring such as discontinuation of filgotinib will be recorded.

8.4. Data Sources

8.4.1. ARTIS

SRQ and ARTIS

A description of ARTIS is provided in Section 6.2. Details of data linkage is provided below. Furthermore, SRQ also provides 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 (EULAR) response criteria, and the American College of Rheumatology criterion of improvement (American College of Rheumatology 2050) 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, 3, and 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.

A) Swedish Nationwide Register Linkages

The register linkage has many advantages in providing data on all comorbidities that have been diagnosed. Importantly, it also allows for obtaining data on comparator cohorts, so that any potential risk increases can be evaluated considering 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.

B) 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 International Statistical Classification of Diseases and Related Health Problems (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% countrywide 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 register data indicate a positive predictive value for a register-based diagnosis of RA around 90% (S. Eriksson et al., 2013; Knight et al., 2008).

C) The Swedish Cancer Register

The Swedish Cancer Register was established in 1958 and contains information on date of cancer (and some selected precancers) 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).

D) 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.

E) The Cause of Death Register

The Cause of Death Register is a national register containing information on date and cause of death (underlying and contributory) for all deceased residents, including deaths among Swedish residents who died abroad. The register 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 3digit level of the ICD-coded underlying cause of death.

F) 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 register will be used to identify the general population comparison cohorts, and to censor subjects who die or emigrate during follow-up.

8.4.2. 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 for this study is recorded by BIOBADASER at (1) baseline as a part of the patient's routine consultations, and (2) during follow-up 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).

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.

8.4.3. 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.

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 Medical Dictionary for Regulatory Activities (MedDRA) system, a licensed copy of which is obtained annually.

8.4.4. 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.

The validity of the RA diagnosis in DANBIO, is >80%, and has been described elsewhere (Hallager 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 3-digit level.

In addition, DANBIO will link registry patients to national health and demographic registers in Denmark for additional data.

A) The Civil Registration System (CRS) of Denmark

Since 1968, each person residing in Denmark is given a unique identification number, the central person registration (CPR) number, which serves as a key reference to the individual in all public registers (Pedersen, 2011; Pedersen et al., 2006). The CPR number is used to link individual data from the registers.

B) The Danish National Patient Register (DNPR)

The register contains data on all hospital contacts since 1976. The data available today includes inpatient hospitalization, emergency room visits, outpatient hospital visits, admission and discharge dates, all surgical procedures, and all diagnosis codes. The diagnoses are based on international classification of disease, Version 10 (ICD 10 codes).

C) The Danish National Database of Reimbursed Prescriptions

The Danish health care system provides partial reimbursement of almost all prescription medications in Denmark. Since 2004, information on all reimbursed prescriptions has been gathered in the Danish National Database of Reimbursed Prescriptions. Medication administration in hospitals is not registered by CPR numbers, and this information can therefore not be used for individual level analyses. The medicinal products are classified according to the World Health Organization Anatomical Therapeutic Classification System (ATC) coding system (Pottegård et al., 2017; Sørensen et al., 1995; Sørensen & Larsen, 1994).

D) Statistics Denmark

Statistics Denmark (http://www.dst.dk) was established in 1850. The institution collects detailed socioeconomic information on all Danish inhabitants regarding education, occupation, economics, etc., has a copy of the national health registers; and makes the data available for research.

E) The Danish National Register of Causes of Death

Since 1875, the National Board of Health has maintained this register of deaths among Danish inhabitants dying in Denmark, and since 1970 the records have been computerized. From 1994, the classification of cause of death was based on ICD 10 codes (Helweg-Larsen, 2011). Data are made available for research by electronical access to a pseudonymized data copy via a safe and password protected data portal at the Danish Health Data Authority (https://sundhedsdatastyrelsen.dk), or at Statistics Denmark (above). Besides the public registers, there is a range of clinical databases available for register-based research.

8.4.5. RABBIT

This study will be conducted in the RABBIT registry using its data sources. The data undergoes 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.

8.5. Study Size

This is a descriptive study without prespecified hypotheses. The goal is to obtain data on all patients who initiate filgotinib during the observational period and thus the numbers will be dictated by the number of filgotinib patients observed in the participating clinics. For illustrative purposes, by applying the rule-of-3 (Hanley & Lippman-Hand, 1983) and assuming an underlying proportion of [any] contraindication of 1%, implies that contraindication would be detected with a certainty of 95% for a sample size of 300 patients; if the underlying proportion of contraindication is 2%, then a sample of 150 patients would suffice (see Table 10).

Table 10 Sample Size Requirements to Detect Contraindication with 95% Certainty

Underlying Proportion of Contraindication	Sample Size to Detect Contraindication
1%	300
2%	150
3%	100
4%	75
5%	60

In terms of precision, if the proportion of patients at high risk of MACE, for example, is assumed to be 10% among a sample size of 300 users of filgotinib, then this will be estimated with a precision (standard error) of 1.7% resulting in a 95% confidence interval (CI) of 6.6% to 13.4% (Altman, 1991). Other scenarios of precision are provided in the following table.

Table 11 Standard Error by Study Size and Underlying Proportion

Proportion*	Study Size			
	200	300	400	500
2%	1.0%	0.8%	0.7%	0.6%
5%	1.5%	1.3%	1.1%	1.0%
10%	2.1%	1.7%	1.5%	1.3%
15%	2.5%	2.1%	1.8%	1.6%

* Proportion of patients at high risk of MACE, VTE or serious and opportunistic infection.

8.6. Data Management

The study will be conducted by making use of secondary data collected prospectively by the individual registries. Each registry has its own data management processes.

8.6.1. ARTIS

As previously described, health and demographic information within Sweden is collected in a series of registers 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 registers is possible. The registers are maintained by

governmental bodies (the main registers 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.

8.6.2. BIOBADASER

Data will be entered in an online application designed ad hoc 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.

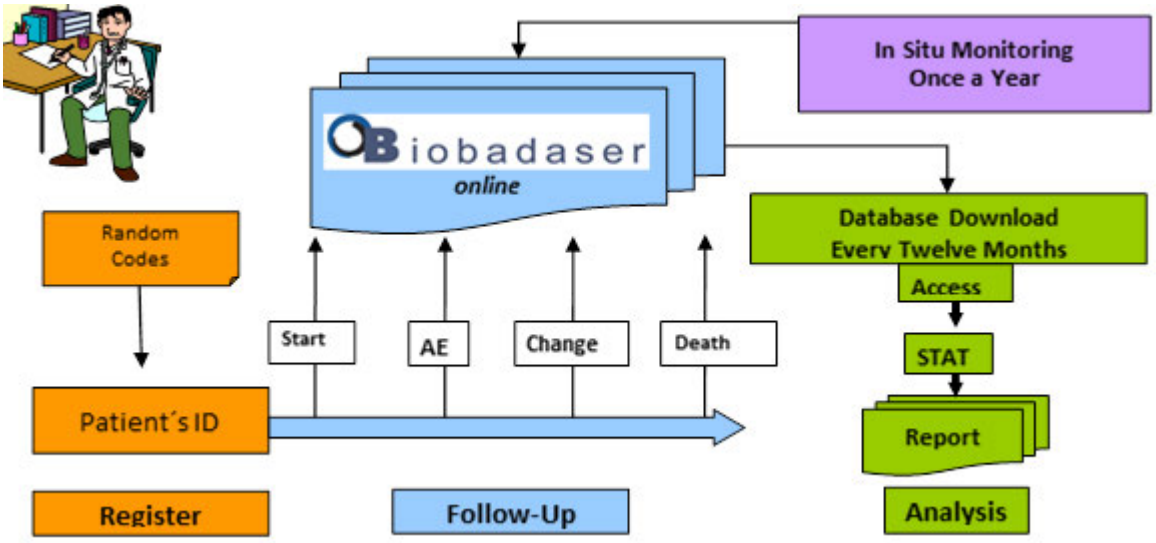


Figure 4 Flowchart Showing the Data Management Process in BIOBADASER

8.6.3. BSRBR-RA

This study is conducted by making secondary use of data collected by BSRBR-RA, which has an established data management process.

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.

8.6.4. DANBIO

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.

8.6.5. RABBIT

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 case report forms (CRFs) (physician and patient questionnaires) are sent by fax to the German rheumatic-disease research center (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, backups are made on a weekly basis.

8.7. Data Analysis

Detailed methodology for the analyses of data included in this study will be documented in the statistical analysis plan, which will be created by the investigators from the 5 registries, dated, filed, and archived by the MAH. Data analysis summarized in the protocol may be modified in the statistical analysis plan to reflect usage of the most up-to-date methodology used by the different registries.

Data from this non-interventional study will be summarized using univariate descriptive statistical methods. Categorical variables will be summarized by number and percentage of patients in each categorical definition and include 95% CIs. Counts for missing values will be also tabulated but missing values will not be considered in the percentages. Continuous variables

will be summarized descriptively (mean, standard deviation, and median, lower quartile, upper quartile, minimum, maximum, 95% CIs).

Follow-up

Among women of childbearing potential (aged 18-49 years) who start filgotinib, the number and proportion who become pregnant will be reported. Similarly, the number and proportion of patients who have a diagnosis of TB or who are administered a live attenuated vaccine will be reported. The proportion of patients who have a test for lipids at 12 weeks since initiation of filgotinib will be reported; we will not evaluate the lipid levels.

Should a VTE event occur, subsequent changes to filgotinib use will be reported (persistence or discontinuation).

All statistical analyses will be performed by the registries using SAS (ARTIS, DANBIO, RABBIT) or STATA (BIOBADASER, BSRBR-RA).

Reports

Two study reports are envisaged: an interim report at approximately 33 months after start of data collection (24 months after start of data collection + at least 9 months for running the analyses and drafting the report) and a final report at approximately 60 months after start of data collection (48 months after start of data collection + 12 months for running the analyses and drafting the report). The interim report will comprise the baseline and follow-up results from all patients initiating filgotinib since start of data collection until month 24. The final report will comprise the baseline and follow-up results of all patients initiating filgotinib since start of data collection until month 48.

As the timing of filgotinib reimbursement and implementation of the aRMMs and identification of the first identified filgotinib user will differ across the 5 countries of interest, the individual registry reports will have different timelines. The timelines for the consolidated interim and final report outlined in the paragraph above are triggered by the registry that last identified the first patient using filgotinib after launch/commercial availability for the treatment of RA and implementation of the aRMMs.

8.8. Quality Control

Each register performs its own quality control. For more details, see following sections.

8.8.1. ARTIS

ARTIS works mainly with data from the SRQ, a quality-of-care register 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 remain.

8.8.2. BIOBADASER

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.
- The application contains filters that limit unreliable data entry (such as data outside permissible range).

8.8.3. BSRBR-RA

The BSRBR-RA data undergo regular validation checks both manually and automatically.

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.

8.8.4. DANBIO

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.

8.8.5. RABBIT

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 1 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.

8.9. Limitations of the Research Methods

This non-interventional PASS uses data collected by 5 well-established European rheumatology registries (ARTIS, BIOBADASER, BSRBR-RA, DANBIO and RABBIT) and captures data at the initiation of filgotinib. The accuracy of the data depends mainly on the professional who records the data and the patient’s responses. This is important given that the study examines medical history which may not be available in the clinical records and thus relies on memory. Furthermore, not all information that is relevant in the context of this DUS (e.g. blood tests and results) may be captured by all registries.

Despite the strengths of this non-interventional DUS using a cohort design, data must be evaluated considering their limitations. For example, consistent with most observational studies, the possibility of channeling biases, endpoint misclassification are of concern.

Any non-interventional study can suffer from bias, specifically, selection bias. However, this study aims to capture all patients initiating filgotinib in the observational period. As all patients are captured, this study will reflect the clinical practice and patient characteristics of these patients.

8.10. Other Aspects

8.10.1. Joint Investigator/Sponsor Responsibilities

8.10.1.1. 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.

9. PROTECTION OF HUMAN SUBJECTS

This study involves data that exist in an anonymized structured format and contain no patient personal information.

9.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The study will be conducted in accordance with the EMA – Guideline on GVP Module VIII – Post-Authorisation Safety Studies, including archiving of essential documents.

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

9.2.1. 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 patients cannot be identified, no IRB/IEC review will be obtained by the MAH.

The ARTIS register 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.

9.2.2. 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.

9.2.3. 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 patients 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.

9.2.4. DANBIO

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

9.2.5. 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.

9.3. Informed Consent

9.3.1. 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.

9.3.2. 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.

9.3.3. 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).

The BSRBR-RA protocol and study documentation has been approved by the North West 5 Research Ethics Committee (Ref 00/8/053). All study annual ethical reports and study amendments are available at www.bsrbr.org.

9.3.4. DANBIO

According to Danish law, informed consent is not required for this kind of data. DANBIO is subject to strict rules and regulations regarding the maintenance, analysis and reporting of personal data.

9.3.5. 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.

9.4. 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.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

This is a non-interventional PASS making secondary use of existing data within 5 European registries (ARTIS, BIOBADASER, BSRBR-RA, DANBIO, and RABBIT), where individual patient data are de-identified. Therefore, the MAH will not collect or report individual case safety reports in an expedited fashion. All the safety data are collected by the registries. Individual AEs will not be solicited in this study Safety findings will be presented in aggregate in the interim and final study report (as part of filgotinib PASS GS-EU-417-9047).

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Study Report and Publications

Individual study reports will be provided by each registry after 33 months (interim) and 60 months (final) of identifying the first patient exposed to filgotinib in the respective registry following commercial availability and implementation of the aRMMs in the corresponding country. The consolidated interim and final study 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 aRMM assessments may be developed by each individual registry for external publication purposes.

12. 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. *Seminars in Arthritis and Rheumatism*, *36*(3), 182–188. https://doi.org/10.1016/j.semarthrit.2006.08.006

Altman, D. (1991). *Practical statistics for medical research*. Chapman & Hall/CRC.

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. *Annals of the Rheumatic Diseases*, *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 and Rheumatism*, *60*(11), 3180–3189. https://doi.org/10.1002/art.24941

Bahl, V., Hu, H. M., Henke, P. K., Wakefield, T. W., Campbell, D. A., & Caprini, J. A. (2010). A validation study of a retrospective venous thromboembolism risk scoring method. *Annals of Surgery*, *251*(2), 344–350. https://doi.org/10.1097/SLA.0b013e3181b7fca6

Barlow, L., Westergren, K., Holmberg, L., & Talbäck, M. (2009). The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncologica (Stockholm, Sweden)*, *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]. *Reumatologia Clinica*, *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 and Rheumatism*, *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. *Annals of the Rheumatic Diseases*, *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. *Annals of the Rheumatic Diseases*, *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. *Annals of the Rheumatic Diseases*, *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. *Annals of the Rheumatic Diseases*, *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. *Clinical and Experimental Rheumatology*, *32*(5 Suppl 85), S-147-149.

Eriksson, S., Graf, E. H., Dahl, V., Strain, M. C., Yukl, S. A., Lysenko, E. S., Bosch, R. J., Lai, J., Chioma, S., Emad, F., Abdel-Mohsen, M., Hoh, R., Hecht, F., Hunt, P., Somsouk, M., Wong, J., Johnston, R., Siliciano, R. F., Richman, D. D., … Siliciano, J. D. (2013). Comparative analysis of measures of viral reservoirs in HIV-1 eradication studies. *PLoS Pathogens*, *9*(2), e1003174. https://doi.org/10.1371/journal.ppat.1003174

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. *Rheumatology (Oxford, England)*, *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 and Rheumatism*, *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 and Rheumatism*, *48*(8), 2122–2127. https://doi.org/10.1002/art.11137

Hallager, S., Ladelund, S., Christensen, P. B., Kjær, M., Thorup Roege, B., Grønbæk, K. E., Belard, E., Barfod, T. S., Madsen, L. G., Gerstoft, J., Tarp, B., Krarup, H. B., & Weis, N. (2017). Liver-related morbidity and mortality in patients with chronic hepatitis C and cirrhosis with and without sustained virologic response. *Clinical Epidemiology*, *9*, 501–516. https://doi.org/10.2147/CLEP.S132072

Hanley, J. A., & Lippman-Hand, A. (1983). If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA*, *249*(13), 1743–1745.

Helweg-Larsen, K. (2011). The Danish Register of Causes of Death. *Scandinavian Journal of Public Health*, *39*(7 Suppl), 26–29. https://doi.org/10.1177/1403494811399958

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

Hippisley-Cox, J., Coupland, C., Vinogradova, Y., Robson, J., Minhas, R., Sheikh, A., & Brindle, P. (2008). Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ (Clinical Research Ed.)*, *336*(7659), 1475–1482. https://doi.org/10.1136/bmj.39609.449676.25

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. *Clinical Epidemiology*, *8*, 737–742. https://doi.org/10.2147/CLEP.S99490

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

Krabbe, S., Grøn, K. L., Glintborg, B., Nørgaard, M., Mehnert, F., Jarbøl, D. E., Østergaard, M., & Hetland, M. L. (2021). Risk of serious infections in arthritis patients treated with biological

drugs: a matched cohort study and development of prediction model. *Rheumatology (Oxford, England)*, *60*(8), 3834–3844. https://doi.org/10.1093/rheumatology/keaa876

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 (Clinical Research Ed.)*, *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. *Annals of the Rheumatic Diseases*, *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 Research & Therapy*, *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. *Annals of the Rheumatic Diseases*, *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. *European Journal of Epidemiology*, *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 Radiologica. Oncology*, *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. *Annals of the Rheumatic Diseases*, *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. *Annals of the Rheumatic Diseases*, *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. *Annals of the Rheumatic Diseases*, *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. *Annals of the Rheumatic Diseases*, *70*(4), 624–629. https://doi.org/10.1136/ard.2010.133371

Pedersen, C. B. (2011). The Danish Civil Registration System. *Scandinavian Journal of Public Health*, *39*(7 Suppl), 22–25. https://doi.org/10.1177/1403494810387965

Pedersen, C. B., Gøtzsche, H., Møller, J. O., & Mortensen, P. B. (2006). The Danish Civil Registration System. A cohort of eight million persons. *Danish Medical Bulletin*, *53*(4), 441–449.

Pottegård, A., Schmidt, S. A. J., Wallach-Kildemoes, H., Sørensen, H. T., Hallas, J., & Schmidt, M. (2017). Data Resource Profile: The Danish National Prescription Registry. *International Journal of Epidemiology*, *46*(3), 798–798f. https://doi.org/10.1093/ije/dyw213

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. *Annals of the Rheumatic Diseases*, *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. *Reumatologia Clinica*, *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. *Clinical Epidemiology*, *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 and Rheumatism*, *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 Research & Therapy*, *17*, 212. https://doi.org/10.1186/s13075-015-0728-9

Smolen, J. S., Aletaha, D., & McInnes, I. B. (2016). Rheumatoid arthritis. *Lancet (London, England)*, *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., … 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 Research & Therapy*, *12*(2), R42. https://doi.org/10.1186/ar2951

Sørensen, H. T., & Larsen, B. O. (1994). A population-based Danish data resource with possible high validity in pharmacoepidemiological research. *Journal of Medical Systems*, *18*(1), 33–38. https://doi.org/10.1007/BF00999322

Sørensen, H. T., Steffensen, F. H., Ejlersen, E., Møller-Petersen, J., & Kristensen, K. (1995). Research in the Danish health service system: completeness and validity of prescription data, illustrated by analysis of utilization of oral anticoagulants. *The International Journal of Risk & Safety in Medicine*, *7*(1), 33–41. https://doi.org/10.3233/JRS-1995-7104

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)? *Scandinavian Journal of Rheumatology*, *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. *Annals of the Rheumatic Diseases*, annrheumdis-2020-219213. https://doi.org/10.1136/annrheumdis-2020-219213

Zink, A., Manger, B., Kaufmann, J., Eisterhues, C., Krause, A., Listing, J., & Strangfeld, A. (2014). Evaluation of the RABBIT Risk Score for serious infections. *Annals of the Rheumatic Diseases*, *73*(9), 1673–1676. https://doi.org/10.1136/annrheumdis-2013-203341

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmaco-epidemiological 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 authorization 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-authorisation cohort safety study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca®) use in patients with moderate to severe active rheumatoid arthritis within European registries

EU PAS Register® number: GLPG0634-CL-408
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]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	Section 5
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

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

Comments:

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	Section 8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	Section 8.1
3.3	Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒	☐	☐	Section 7 Section 8.7
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))	☐	☐	☒	--
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)	☐	☐	☒	--

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	Sections 8.1, 8.2
4.2	Is the planned study population defined in terms of:				8.4
	4.2.1 Study time period	☒	☐	☐	Section 8.1, 8.2.6
	4.2.2 Age and sex	☒	☐	☐	Section 8.2.6
	4.2.3 Country of origin	☒	☐	☐	Section 8.1, 8.2 Section 8.2.6
	4.2.4 Disease/indication	☒	☐	☐	Section 8.2.6
	4.2.5 Duration of follow-up	☒	☐	☐	Section 8.1, 8.2.6
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 8.4, 8.2.6 to 8.2.8

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)	☐	☐	☒	--
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)	☐	☐	☒	--
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?	☐	☐	☒	--

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 8.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Section 8.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	Section 8.8
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 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	Section 8.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	Section 8.9

Comments:

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

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 8.4
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 8.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	Section 8.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Section 8.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 8.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	Section 8.3
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 8.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates and other characteristics?	☒	☐	☐	Section 8.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	Section 8.3

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 8.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	Section 8.5
10.3 Are descriptive analyses included?	☒	☐	☐	Section 8.7
10.4 Are stratified analyses included?	☒	☐	☐	Section 8.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	--
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 8.6
11.2 Are methods of quality assurance described?	☒	☐	☐	Section 8.6, 8.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	--

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	Section 8.9
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 8.1, 8.5

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 9.2
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	Section 9.2
13.3 Have data protection requirements been described?	☒	☐	☐	Section 9.2

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: 2 February 2022

Signature: _____

ANNEX 3. REFERENCE SAFETY INFORMATION

Please refer to the SmPC:

https://www.ema.europa.eu/en/documents/product-information/jyseleca-epar-product-information_en.pdf

ANNEX 4. DEFINITION OF BASELINE DISEASES IN ARTIS, BIOBADASER, BSRBR-RA, DANBIO, AND RABBIT

The following medical code-lists were created for the long-term safety PASS (GS-EU-417-9047) and were reviewed by the registries.

	BSRBR-RA, RABBIT, BIOBADASER	**ARTIS, DANBIO**
Safety Risk	**Operationalization (final list to be defined based on reported endpoints in each register)**	**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 ICD10codes below. If main diagnosis is RA, contributory diagnoses are also considered. A00B99 (excluding A33 and A50), D73.3, E32.1, G00G02, G04.2, G05G07, H00.0, H44.0, H60.0H60.3, H66H67, H70, I30.1, I40.0, J00J22, J32, J34.0, J36, J39.0J39.1, 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, L00L08, L30.3, M00M01, M46.2M46.5, 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 multidermatomal, 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 ICD10codes A02, A15A19, 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.

Nonmelanoma 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 ICDO/2 code C44 and D04, plus ICD7 code 191, and all basal cell cancers recoded in the register's subcomponent on basal cell cancers.
Gastrointestinal (GI) perforation	10000099 Abdominal wall abscess; 10000285 Abscess intestinal; 10000582 Acquired tracheooesophageal fistula; 10002156 Anal fistula; 10002157 Anal fistula excision; 10002248 Anastomotic ulcer perforation; 10002924 Aortoduodenal 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 Intraabdominal haemorrhage; 10061820 Diverticular perforation; 10061975 Gastrointestinal ulcer	Main diagnosis recorded in the inpatient component of the Patient Register listing ICD10codes: 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. 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.

	perforation; 10062065 Perforated ulcer; 10062070 Peritonitis bacterial; 10062570 Enterovesical fistula; 10065713 Gastric fistula; 10065879 Gastrointestinal anastomotic leak; 10066870 Aortooesophageal fistula; 10066892 Rectourethral fistula; 10067091 Gastropleural fistula; 10068792 Gastrosplenic fistula; 10071647 Infectious peritonitis.	
MACE	Fatal and nonfatal : 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 MillardGubler 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. Fatal only: 10002886 Aortic aneurysm rupture; 10003173 Arterial rupture; 10003210 Arteriosclerosis; 10003212 Arteriosclerosis moenckebergtype; 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	Combines MI, stroke, and fatal cardiovascular events: I00I99 as main cause of death, or I20.0, I21, I60I64 as diagnosis in in or outpatient care.

	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 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 outpatient component, of the following ICD10 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.	Patients who will initiate treatment with statins and other lipid-lowering drugs.

	BSRBR-RA: Patients who will initiate treatment with statins or other lipid-lowering drugs. RABBIT: Hyperlipidemia reported as adverse event by the treating physician.	

Other medical history

Disease	Data source	ICD10
Malignancy	The Cancer register	All except benign tumors
Infection	Main diagnoses from the Inpatient component of Patient Register.	A00B99, D73.3, E06.0, E32.1, G00G02, G04.2, G05G07, H00.0, H44.0, H60.0H60.3, H66H67, H70, I30.1, I40.0, J00J22, J32, J34.0, J36, J38.3, J39.0J39.1, 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, L00L08, L30.3, M00M01, M46.2M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N10, N11, N12, 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
Renal impairment		N18, N18.1, N18.2, N18.3, N18.4, N18.5
Knee or hip prosthesis	Operation codes from the Patient register	NGB, NFB
Diabetes	The Patient Register	E10E14, O24
Myocardial infarction	The Patient Register	I21, I22

SIGNATURE PAGE – INVESTIGATOR

Study Title: Non-interventional post-authorization cohort safety study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca®) use in patients with moderate to severe active rheumatoid arthritis within European registries

CSP Version: 1.0 **Date**: 02-Feb-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 Practices.

Investigator Name	Signature	Date

SIGNATURE PAGE – SPONSOR

Study Title: Non-interventional post-authorization cohort safety study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca®) use in patients with moderate to severe active rheumatoid arthritis within European registries

CSP Version: 1.0 **Date**: 02-Feb-2022

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

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

Medical Leader	Signature	Date

Signature Page for glpg0634-cl-408-protocol 21839

Approval	PPD Lead Medical Safety 02-Feb-2022 14:27:13 GMT+0000

Approval	PPD erson for Pharmacovigilance Medical Safety 02-Feb-2022 15:37:22 GMT+0000

Signature Page for glpg0634-cl-408-protocol43952_42085_63800