Galápagos
Pioneering for patients

NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Project Number:	GLPG0634 (filgotinib)		
Study Number:	GLPG0634-CL-417 (previously GS-EU-418-5981)		
Study Title:	Non-interventional post-authorization prospective cohort study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca®) use in patients with ulcerative colitis: a European multi registry-based study		
Development Phase:	4		
Status:	Final		
Version:	3.0	Date:	25-Jan-2024
EU PAS Register No:	To be determined	ClinicalTrials.gov identifier:	Not applicable
Active Substance:	Filgotinib (ATC code: L04AA45)		
Medicinal Product:	Jyseleca® (filgotinib)	Product Reference:	EU/1/20/1480
Procedure Number:	EMEA/H/C/005113/MEA/017		
Joint PASS:	No		
Research Question and Objectives:	To evaluate the effectiveness of the additional risk minimization measures (after the EC decision on Article 20 on JAKi's) in adult patients with ulcerative colitis initiating treatment with filgotinib		
Country (-ies) of study:	Netherlands, Spain, Sweden		
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		
Qualified Person for Pharmacovigilance (QPPV):	Name: PPD Email: PPD		

Confidentiality Statement

The information contained in this document is privileged and confidential. It is the property of Galapagos NV and may not be used, disclosed, reproduced or otherwise disseminated within your organization or communicated to any third parties without the express written authorization of Galapagos NV.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ALC	absolute lymphocyte count
ANC	absolute neutrophil count
aRMM	additional risk minimization measure
BMI	body mass index
CD	Crohn's disease
CI	confidence interval
CMO	Commissie Mensgebonden Onderzoek
CRP	C-reactive protein
CV(D)	cardiovascular (disease)
DHPC	direct healthcare professional communication
DUS	drug utilization study
EC	European Commission
eCRF	electronic case report form
EMA	European Medicines Agency
EMR	electronic medical record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ENEIDA	Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales (Nationwide study on genetic and environmental determinants of inflammatory bowel disease)
ES	Spain (España)
EU	European Union
GETECCU	Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (Spanish Working Group on Crohn's Disease and Ulcerative Colitis)
GVP	Good Pharmacovigilance Practices
Hb	hemoglobin
HCP	healthcare professional
HBI	Harvey-Bradshaw Index
IBD	inflammatory bowel disease
IC	informed consent
ICC	Initiative on Crohn's and Colitis
ICD	International Classification of Diseases
JAK(i)	Janus kinase (inhibitor)
KI	Karolinska Institute
MACE	major adverse cardiovascular event
MAH	marketing authorization holder
MEMIC	Center for data and information management at the Faculty of Health, Medicine and Life Sciences of Maastricht University
MHRA	Medicines and Healthcare products Regulatory Agency
na	not applicable
NCSP	NOMESCO Classification of Surgical Procedures

NL	the Netherlands
NOMESCO	Nordic Medico-Statistical Committee
NPR	National Patient Register
PAC	patient alert card
PASS	post-authorization safety study
PDR	Prescribed Drug Register
PE	pulmonary embolism
PRAC	Pharmacovigilance Risk Assessment Committee
PY	person-year
QPPV	Qualified Person for Pharmacovigilance
RCT	randomized clinical trial
RTI-HS	Research Triangle Institute Health Solutions
SAP	statistical analysis plan
SCCAI	Simple Clinical Colitis Activity Index
SmiNet	Swedish Contagious Disease Register
SmPC	Summary of Product Characteristics
STAT	signal transducer and activator of transcription
SWE	Sweden
SWIBREG	Swedish National Quality Registry for Inflammatory Bowel Disease
TB	tuberculosis
TNF	tumor necrosis factor
UC	ulcerative colitis
VTE	venous thromboembolism

2. RESPONSIBLE PARTIES

Table 1 Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Marketing Authorization Holder	Galapagos NV Generaal De Wittelaan L11 A3 2800 Mechelen Belgium	PPD
Pharmacoepidemiology Leader	PPD	PPD
Medical Director	PPD	PPD
ENEIDA Principal Investigators	PPD	
RTI Leader (scientific service provider for ENEIDA)	PPD	PPD
ICC Principal Investigator	PPD	PPD
SWIBREG Principal Investigator	PPD	PPD
Pharmacovigilance	PPD	PPD

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
EU QPPV	PPD	PPD

ENEIDA = Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales (Nationwide study on genetic and environmental determinants of inflammatory bowel disease); EU = European Union; ICC = Initiative on Crohn's and Colitis; QPPV = Qualified Person for Pharmacovigilance; RTI = Research Triangle Institute; SWIBREG = Swedish National Quality Registry for Inflammatory Bowel Disease

3. ABSTRACT

Study Title: Non-interventional post-authorization prospective cohort study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca®) use in patients with ulcerative colitis: a European multi registry-based study

Protocol version: v3.0
Date: 25-January-2024
Author, Affiliation: PPD

Rationale and Background:

Ulcerative colitis (UC) is an immune-mediated, chronic idiopathic inflammatory bowel disease (IBD) of the colon. It shows continuous mucosal inflammation that may extend from the rectum to the more proximal colon leading to bloody diarrhea, frequent bowel movements, variable degrees of abdominal pain, and rectal tenesmus.

Filgotinib (Jyseleca®) is an oral Janus kinase (JAK) 1 preferential inhibitor initially approved in the European Union in September 2020 for moderately to severely active rheumatoid arthritis and in November 2021 also for the treatment of adult patients with moderately to severely active UC who have an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.

Additional risk minimization measures (aRMMs) are in place to mitigate important identified and potential risks associated with filgotinib use. These include a healthcare professional (HCP) Guide designed to increase awareness among HCPs by delivering specific information on contraindications, and warnings and precautions (in conjunction with the information available in the filgotinib summary of product characteristics [SmPC]), and a patient alert card (PAC) to enhance awareness of risks and early signs and symptoms relating to specific adverse drug reactions and the best course of action to take. In the context of the review of the safety of JAK inhibitors (JAKi's) for treatment of various chronic inflammatory disorders (including UC) started by the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004 on 10 February 2022 and completed on 10 March 2023 (EC decision date), HCP Guide, PAC and SmPC have been modified specifically with respect to the warnings and precautions section, especially for patients ≥65 years of age, and patients with risk factors for venous thromboembolism (VTE), major adverse cardiovascular events (MACE), and malignancy (including non-melanoma skin cancer [NMSC]).

Research Question and Objectives

Information on prescribing of filgotinib for UC under real-world conditions is scarce, specifically, in the context of the updated SmPC and HCP Guide after implementation of Article 20 decisions on JAKi's. Therefore, to describe physicians' adherence to the prescribing information of filgotinib in real-world clinical practice, a drug utilization study (DUS) is being performed using secondary data collected from 3 European IBD registries (from the Netherlands, Spain, Sweden; see 'Data Sources' for more details).

This longitudinal DUS aims to evaluate the effectiveness of the aRMMs by assessing how HCPs prescribing filgotinib adhere to the updated filgotinib SmPC and HCP Guide with a specific focus on aRMMs after the EC Article 20 decision date (10 March 2023).

Objectives

a) To describe the characteristics of patients treated with filgotinib in terms of:
- Demographics (e.g., age and sex)
- Comorbidities and prior and current medication use

b) To evaluate prescribers' adherence to the filgotinib aRMMs, specifically:
- Compliance to the recommended posology (average daily dose) and duration of use

• Compliance to recommendations for patient screening and laboratory monitoring prior to and during treatment • Compliance to recommendations for use in patients with moderate to severe chronic renal impairment/end stage renal disease or severe hepatic impairment • Compliance to recommendations for limitations of use, including: - Use in patients with risk factors for venous thromboembolism (VTE) - Use in patients aged 65 years and older - Use in patients with risk factors for cardiovascular (CV) disease - Use in patients with risk factors for malignancy - Use in patients with risk factors for serious infections - Use in patients with concomitant use of other potent immunosuppressants - Use of live attenuated vaccines - Contraindicated use • Compliance with discontinuation of filgotinib treatment in patients experiencing VTE
Study Design: DUS using a non-interventional, post-authorization, prospective, multicountry, registry-based, longitudinal follow-up (cohort) design with secondary use of data collected from 3 European IBD registries (see 'Data Sources' for more details). The study fulfills the criteria of a non-interventional post-authorization safety study (PASS [category 3]) in accordance with the commitment to the European Medicine Agency (EMA) and to the Medicines and Healthcare products Regulatory Agency (MHRA) from the United Kingdom. The overall study duration will be 4 years with a start of data collection after the EC decision date on Article 20 for JAKi's (i.e. 10 March 2023).
Population: The study population will include consecutive adult patients (≥18 years of age) of all sexes with prevalent or incident UC identified from 3 registries being initiated on filgotinib after the EC decision date on Article 20.
Variables: The study will include baseline and follow-up information relevant for the specific aRMM as well as information on the distribution of risk factors indicative of a high risk of MACE, VTE, malignancy, or serious and opportunistic infections (as per availability of variables in each registry).
Data Sources: The study will be conducted within 3 European IBD registries: (i) the Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales (Nationwide study on genetic and environmental determinants of inflammatory bowel disease [ENEIDA]) Registry, a large prospectively maintained Spanish database promoted by the Spanish Working Group on Crohn's and Ulcerative Colitis (GETECCU); (ii) the Initiative on Crohn's and Colitis (ICC) Registry, a nationwide, observational registry with prospective follow-up of patients with IBD starting prespecified IBD therapies from the Netherlands; and (iii) the Swedish Inflammatory Bowel Disease (SWIBREG) Register, a nationwide, prospective, observational IBD quality registry in Sweden. Each registry will use its own data sources (including linkage to other data sources if available) enriched with supplemental secondary data collection if needed and where applicable.

Study Size:

This is a descriptive DUS without prespecified hypotheses. Up to 500 eligible consecutive patients will be included per registry.

Data Analysis:

The patients' baseline and follow-up characteristics (e.g. age, sex, comorbidities, prior and current comedication use) will be summarized to assess adherence to the aRMMs with a focus on posology, contraindications, special warnings and precautions, monitoring, as well as the proportion of patients at high risk of MACE, VTE, malignancy, or severe and opportunistic infections. Data will be summarized using univariable descriptive statistical methods. Categorical variables will be summarized by number and percentage of patients in each categorical definition including 95% confidence intervals (CIs). Continuous variables will be summarized descriptively (mean, standard deviation, and median, lower quartile, upper quartile, minimum, maximum, 95% CIs).

All statistical analyses will be performed by each registry or its local contracted scientific service provider. Detailed information on the analyses will be provided in the statistical analysis plan (SAP).

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. The final study report will be submitted no later than 12 months after the end of overall data collection.

Study reports may also be used in regulatory communications in countries outside of Europe.

Protocol (first) submission:	Within 18 months after EC approval of filgotinib for the treatment of UC (12-May-2023 at the latest)
Registration in the EU PAS register:	Within 4 months after protocol approval
Start of data collection:	With the first patient identified per register after the EC decision date on Article 20 on JAKi's (i.e. after 10 March 2023)
End of interim data collection*:	Q1 2027
End of data collection*:	Q1 2029
Interim report submission (with 2 years of data):	End of interim data collection + 9 months (Q4 2027)
Final study report submission (with 4 years of data):	End of data collection + 12 months (Q1 2030)

EU = European Union; PAS = post-authorization study; UC = ulcerative colitis
* corresponds to the date at which the analytical dataset to perform the statistical analyses is completely available (this would be after chart abstraction in ENEIDA [won't be done for the interim report] and data linkage across the Swedish registers [usually linked data for a calendar year become available approximately 13 months after year-end, i.e. in January the year after next])

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices, Good Pharmacovigilance Practices (GVP), and the European Medicines Agency (EMA) guideline on registry-based studies including archiving of essential documents.

4. AMENDMENTS AND UPDATES

Not applicable.

5. MILESTONES

The milestones for the study are presented in Table 2.

Each registry will be deemed to start data collection after the European Commission's (EC) final decision on the Article 20 for Janus kinase inhibitors (JAKi's) (i.e. 10 March 2023; for details, see Section 6) and identification of the first eligible filgotinib patient in the registry.

An interim study report will be provided with data including 24 months of data collection following the study start date; preparation of the interim report will take approximately 9 months. A full analysis will be performed with data including 48 months of data collection; the analyses and drafting of the full report will take approximately 12 months.

Note: SWIBREG will require additional time for linkage data to be available. Thus, the consolidated reports will be created once the last registry has provided its results.

The overall study period will therefore account for the timing of the start of the study, the data collection periods (including chart abstraction), data linkage, data management, data analysis, and submission of the consolidated interim and final report.

Table 2 Milestones

Milestone	Planned Date
Protocol submission (first version)	Within 18 months after European Commission (EC) approval of filgotinib for the treatment of UC (by 12-May-2023 at the latest)
Start of data collection	With the first patient identified per register after the EC decision date on Article 20 on JAKi's (i.e. after 10 March 2023)
End of interim data collection*	Q1 2027
End of data collection*	Q1 2029
Interim report submission (with 2 years of data)	End of interim data collection + 9 months (Q4 2027)
Registration in the EU PAS register	Within 4 months after protocol approval
Final study report submission (with 4 years of data)	End of data collection + 12 months (Q1 2030)

EU = European Union; PAS = post-authorization study; UC = ulcerative colitis
* corresponds to the date at which the analytical dataset to perform the statistical analyses is completely available (this would be after chart abstraction in ENEIDA [won't be done for the interim report] and data linkage across the Swedish registers [usually linked data for a calendar year become available approximately 13 months after year-end, i.e. in January the year after next])

6. RATIONALE AND BACKGROUND

Ulcerative colitis (UC) is an immune-mediated, chronic idiopathic inflammatory bowel disease (IBD) of the colon. It shows continuous mucosal inflammation that may extend from the rectum to the more proximal colon leading to bloody diarrhea, frequent bowel movements, variable degrees of abdominal pain, and rectal tenesmus. The pathogenesis of UC is multifactorial and includes (auto-)immune, genetic, environmental, and gut microbial components (Feuerstein et al., 2019; Gajendran et al., 2019; Ungaro et al., 2017).

UC most commonly affects adults aged 30 to 40 years, without specific sex predominance components (Feuerstein et al., 2019; Gajendran et al., 2019; Ungaro et al., 2017). It is more common in industrialized countries, but there is a worldwide increase in prevalence and incidence, especially in Asia (Feuerstein et al., 2019, 2019; Gajendran et al., 2019; Ungaro et al., 2017; Zhao et al., 2021). In Europe, the overall age- and sex-adjusted annual incidence is around 8.2 per 100000, with higher incidence observed in Western (9.8/100000) versus Eastern European countries (4.6/100000) (Burisch et al., 2014). The prevalence of UC in Europe ranges from 2.4 (Romania) to >600 (UK) per 100000 (Ananthakrishnan, 2015; Brunet et al., 2018; King et al., 2020; Macaluso et al., 2019; Ng et al., 2017).

UC patients experience various comorbidities (Román, 2011) including infections (Côté-Daigneault et al., 2019; Irving et al., 2021; Tosca et al., 2020; Wisniewski et al., 2020), cardiovascular diseases (CVD) (Chen et al., 2022; Shen et al., 2021; Weissman et al., 2020), venous thromboembolism (VTE) (Shen et al., 2021; Weissman et al., 2020), and malignancies (including non-melanoma skin cancer [NMSC]) (Burisch et al., 2022; Greuter et al., 2020; Lo et al., 2021; Shen et al., 2021; Zhou et al., 2019), which may be in addition to, or further worsened by adverse effects in association with drug treatment for UC.

Filgotinib (Jyseleca®) is an oral, adenosine triphosphate-competitive, 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 (Dhillon & Keam, 2020). In addition to their use in rheumatoid arthritis (Harrington et al., 2020), JAKi's have also been studied in IBD including UC (Feagan et al., 2021; Harris & Cummings, 2021; Mannucci et al., 2022; Taneja et al., 2021).

Jyseleca was initially approved in the European Union (EU) for moderately to severely active rheumatoid arthritis in September 2020. In November 2021 Jyseleca additionally received EU approval as induction and maintenance therapy in adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent. This was based on data from the pivotal Phase 2b/3 SELECTION program which provided information on filgotinib's efficacy and safety (D'Amico et al., 2022). Assessment of safety using only data from randomized clinical trials (RCTs) however, is subject to limitations, like the relatively small sample sizes, more restrictive

inclusion and exclusion criteria, and relatively short duration of follow-up. Long-term safety data are therefore needed in patients treated with filgotinib in real-world clinical settings and in patient populations where there are limited RCT data. For this reason, a non-interventional post-authorization safety study (PASS) assessing the long-term safety of filgotinib is being conducted using information from 3 European IBD registries (study ID: GLPG0634-CL-413).

Furthermore, 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 precautions. Moreover, there is a patient alert card (PAC) to enhance awareness of risks and early signs and symptoms relating to specific adverse drug reactions and the best course of action to take.

On 10 February 2022, the Pharmacovigilance Risk Assessment Committee (PRAC) started a review of the safety of JAKi's for treatment of various chronic inflammatory disorders (including UC) under Article 20 of Regulation (EC) No 726/2004 (European Medicines Agency, 2022). This was triggered by the results of the 'Oral Surveillance Study' – an open-label, non-inferiority, post-authorization safety RCT involving patients with active rheumatoid arthritis aged ≥ 50 years and with at least one additional cardiovascular (CV) risk factor. The study suggested an increased risk of major adverse cardiovascular events (MACE) and malignancies in patients treated with the JAKi tofacitinib compared with tumor necrosis factor (TNF)α inhibitor treated patients (Ytterberg et al., 2022).

On 10 March 2023, with the EC's final decision on Article 20, the measures recommended by PRAC to minimize the risk of serious adverse events with JAKi's (including CV conditions, VTE, malignancies and serious infections) were endorsed. It was recommended that JAKi's should only be used in patients aged 65 years or above, those at increased risk of MACE, those who smoke or have done so for a long time in the past, and those at increased risk of malignancies "if no suitable treatment alternatives are available".

Based on the above PRAC recommendations and the approved key concepts in the summary of product characteristics (SmPC) (https://www.ema.europa.eu/en/documents/product-information/jyseleca-epar-product-information_en.pdf), the marketing authorization holder (MAH) of filgotinib updated the existing HCP Guide and the PAC to reflect the changes in SmPC for filgotinib following the EC's final decision on Article 20.

Furthermore, a direct healthcare professional communication (DHPC) was issued to inform prescribers on the identified risks related to serious and opportunistic infections, and the potential risks of malignancies, VTE, and MACE.

The safety information in the HCP Guide provides context and risk management advice for key safety aspects of the SmPC, namely (key safety aspects with updates in the HCP Guide after Article 20 are listed in *italics*):

- Serious and opportunistic infections
- Herpes zoster
- Potential risk of birth defects if filgotinib is taken during pregnancy

- *Potential risk of VTE*
- *Potential risk of MACE*
- *Potential risk of malignancy*
- *Prescribing in elderly patients and in patients with risk factors for VTE, MACE, and malignancy*

The SmPC specifies that the recommended dose for induction treatment in UC is 200 mg once daily. The recommended dose for maintenance treatment is 200 mg once daily. In patients aged 65 years or older or at higher risk of VTE, MACE and malignancy, the recommended dose is 200 mg once daily for the induction treatment which may be prolonged up to Week 22, and 100 mg once daily for maintenance treatment. In case of flare of the disease, the dose may be escalated to 200 mg once daily. For long term treatment, the lowest effective dose should be used (as per SmPC Section 4.2 'Posology and method of administration').

In patients with active tuberculosis (TB), active serious infections, or in women who are pregnant treatment with filgotinib is contraindicated (as per SmPC Section 4.3 'Contraindications').

Additional aspects as per updated SmPC Section 4.4 'Special warnings and precautions for use' are listed below:

Use in patients 65 years of age and older: Considering the increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, filgotinib should only be used in these patients if no suitable treatment alternatives are available.

Infections: As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes.

Malignancy: In patients 65 years of age and older, patients who are current or past long-time smokers, or with other malignancy risk factors (e.g. current malignancy or history of malignancy), filgotinib should only be used if no suitable treatment alternatives are available.

MACE (i.e. fatal and nonfatal CVD events; CVD comprises coronary heart disease [angina, myocardial infarction], congestive heart failure, cerebrovascular disease and peripheral artery disease]): In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic CVD or other CV risk factors, filgotinib should only be used if no suitable treatment alternatives are available.

VTE (includes deep venous thrombosis) and pulmonary embolism [PE]): In patients with CV or malignancy risk factors filgotinib should only be used if no suitable treatment alternatives are available.

In patients with known VTE risk factors other than CV or malignancy risk factors, filgotinib should be used with caution. VTE risk factors other than CV or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilization, use of combined hormonal

contraceptives or hormone replacement therapy, inherited coagulation disorder. Patients should be re-evaluated periodically during filgotinib treatment to assess for changes in VTE risk.

Patients with signs and symptoms of VTE should promptly be evaluated and filgotinib be discontinued in patients with suspected VTE, regardless of dose.

This longitudinal drug utilization study (DUS) is being conducted by the MAH as a Category 3 commitment to the EMA and to the Medicines and Healthcare products Regulatory Agency (MHRA) based on real-word secondary data derived from the same 3 IBD registries used for the filgotinib LTS PASS (GLPG0634-CL-413), namely the Estudio Nacional en Enfermedad Inflamatoria Intestinal sobre Determinantes Genéticos y Ambientales (ENEIDA) Register from Spain, the Initiative on Crohn and Colitis (ICC) Register from the Netherlands, and the Swedish National Quality Registry for Inflammatory Bowel Disease (SWIBREG).

This protocol follows the approach used in the already endorsed DUS for filgotinib in RA (GLPG0634-CL-408), thereby also taking into account prior comments from the PRAC Rapporteur.

7. RESEARCH QUESTION AND OBJECTIVES

Information on prescribing of filgotinib for UC under real-world clinical practice is scarce, specifically, in the context of the updated prescribing information and HCP Guide after implementation of Article 20 decisions on JAKi's.

Therefore, this longitudinal DUS aims to describe physicians' adherence to the prescribing information of filgotinib in real-world clinical practice and to evaluate the effectiveness of the aRMMs by assessing how HCPs prescribing filgotinib adhere to the information provided in the SmPC in conjunction with the information in the HCP Guide with a specific focus on aRMMs implemented after the EC Article 20 decision on JAKi's (i.e. after 10 March 2023).

The objectives of this study are as follows:

a. To describe the characteristics of patients treated with filgotinib in terms of:
- Demographics (e.g., age and sex)
- Comorbidities and prior and current medication use

b. To evaluate prescribers' adherence to the filgotinib aRMMs, specifically:
- Compliance with the recommended posology (average daily dose) and duration of use
- Compliance with recommendations for patient screening and laboratory monitoring prior to and during treatment
- Compliance to recommendations for use in patients with moderate to severe chronic renal impairment/end stage renal disease or severe hepatic impairment
- Compliance with recommendations for limitations of use, including:
    - Use in patients with risk factors for venous thromboembolism (VTE)
    - Use in patients aged 65 years and older
    - Use in patients with risk factors for cardiovascular (CV) disease
    - Use in patients with risk factors for malignancy

  - Use in patients with risk factors for serious infections
  - Use in patients with concomitant use of other potent immunosuppressants
  - Use of live attenuated vaccines
  - Contraindicated use
- Compliance with discontinuation of filgotinib treatment in patients experiencing VTE

8. RESEARCH METHODS

8.1. Study Design

This DUS is based on a non-interventional, post-authorization, prospective, multicountry, registry-based, longitudinal follow-up (cohort) design with secondary use of data collected from 3 European IBD registries. The registries to be used are: (i) the ENEIDA Register from Spain (ES), (ii) the ICC Register from the Netherlands (NL), and (iii) SWIBREG from Sweden (SWE). Data from the 3 European IBD registries may be enriched with additional (secondary) data collection information if needed and applicable. The study fulfills the criteria of a non-interventional PASS (category 3) in accordance with the commitment to the EMA and to the MHRA from the United Kingdom.

The study population will include up to 500 consecutive adult patients of any sex with UC and initiating treatment with filgotinib following implementation of the aRMMs after EC's final decision on Article 20 (decision date: 10 March 2023) per registry.

The observational period will be 4 years starting after the EC decision date on Article 20 (i.e. after 10 March 2023). It will include all follow-up time until dropout for the included patients.

Two reports will be generated: an interim report with 2 years of data collection (to be submitted within 9 months after end of interim data collection), and a final study report with 4 years of data collection (to be submitted within 12 months after end of data collection).

Note: The end of data collection, i.e. the timepoint by which the analytical dataset to perform the statistical analyses is completely available, is highly correlated with the process of chart abstraction (ENEIDA) or data linkage (SWIBREG). Thus, interim and final study reports will not be available within 9 and 12 months, respectively from the end of the observational periods.

In addition, in the ENEIDA registry, the set-up of ethics approvals, contracts and necessary activities (e.g. trainings) with all individual centers before chart abstraction can begin will likely take up to 2 years, based on prior experience in conducting similar PASS in this registry. It is important to keep this in mind for the scope of the interim report since it will be limited to information readily available in the ENEIDA registry (i.e. without supplementing its information with chart abstraction).

The chosen design of a prospective non-interventional registry-based follow-up study allows the investigation of the specific research questions of this DUS using the data collection infrastructure of 3 existing and established IBD registries based on real-world data (European Medicines Agency, 2021). In addition, the 3 data sources have been combined into 1 common

protocol to align the data collection process of this study as much as possible aiming for increased consistency in design (Klungel et al., 2016).

8.2. Setting and Study Population

8.2.1. IBD Registries

8.2.1.1. ENEIDA (ES)

Spain's healthcare system guarantees universal coverage for all residents (N = 47 million) and is principally funded through taxation. Specialist care is provided in specialist care centers and hospitals in the form of outpatient and inpatient care.

Most hospitals in Spain have an electronic medical record (EMR) system that provides access for clinicians to review all care that takes place in the same hospital. Moreover, an increasing number of geographical areas have implemented an EMR system that allows access to all the information generated by public hospitals in the same region. Some also provide access to general practitioner data.

Patients with IBD will typically be followed by their gastroenterologist (specialist) in a hospital outpatient setting on a regular basis. For stable asymptomatic patients, follow-up will be scheduled to happen at least every 2 years, whereas for patients with active moderate to severe UC or with ongoing treatment with biologics, follow-up will happen at least every 6 months, based on clinical guidelines in Spain.

The UC prevalence in Spain has been estimated at around 88 per 100000 population (Marín-Jiménez et al., 2018), the annual incidence at 8.1 per 100000 individuals (Chaparro et al., 2021), which is in line with those reported in other European countries.

As of February 2023, there were 37865 patients with UC enrolled in the ENEIDA registry; between 2000 and 3000 additional patients with UC are enrolled annually in the registry. More than 20000 of the enrolled patients are from centers meeting the criteria for research-quality data. These figures indicate that ENEIDA currently covers about 10% of all existing cases of UC in Spain. However, the registry is likely to enroll a significantly larger proportion of all newly diagnosed patients with UC and of initiators of advanced therapies for UC in Spain.

For specific details on the ENEIDA registry, see Section 8.4.1.

8.2.1.2. ICC (NL)

The Netherlands has a population of approximately 17.2 million inhabitants, with a UC prevalence of approximately 226 per 100000 population (de Groof et al., 2016) and an incidence of around 17.2/100000 person-years (PYs) (Ng et al., 2017). Patients with IBD are typically treated by a gastroenterologist (specialist).

All adult Dutch residents are obliged to purchase basic health insurance from a private firm. The basic package – based on an officially set premium – covers medical and dental care, hospitalization, and a variety of medical appliances, pharmaceuticals, and paramedical care.

Complementing insurance can be purchased by individuals to cover requirements beyond the basic package. Insurance companies are, however, free to set prices, and, unlike the basic package, can reject applicants.

In the ICC Registry, patients with IBD 16 years of age or older, with an established diagnosis of UC or Crohn's Disease (CD), are eligible. Follow-up visits after the initial baseline visit (Week 0) are scheduled on Week 12, 24, 52, and once yearly up to 10 years after initiation of treatment.

If a patient discontinues medication and initiates another treatment that is included in the ICC Registry, the follow-up is scheduled at Week 12, 24, 52, and once yearly.

Patients included in the study should be included in the registry at least 12 weeks prior to analyses.

In total, 20 hospitals are involved in ICC; these include all university hospitals in the Netherlands and multiple large non-university hospitals. Officially, there are 69 hospitals in the Netherlands; this number however includes a lot of small medical centers, which only have small numbers of patients with IBD and often do not prescribe second- or third-line biologics easily. Overall, with the 20 large hospitals that are involved in ICC, it is estimated that ICC covers at least 50% of patients with IBD in the Netherlands.

For more details on the ICC Registry, see Section 8.4.2.

8.2.1.3. SWIBREG (SWE)

Sweden is a Scandinavian country with 10 million residents. Healthcare is publicly funded, and prescription drugs are provided free of charge above an annual threshold of approximately $250 United States dollars (Laugesen et al., 2021).

Health and demographic information are recorded in a series of registers with a very high degree of completeness resulting from the mandatory and semiautomated registration. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born 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, who may perform data linkages and provide de-identified data for research purposes (Laugesen et al., 2021). The UC incidence among Swedish adults for the years 2006 to 2013 was estimated as 20 per 100000 PYs (Everhov et al., 2018). By 2018 there were approximately 51000 prevalent patients with UC in Sweden (Olén et al., 2020), yielding a UC prevalence of approximately 500 per 100000 population.

Patients with UC are typically treated by gastroenterologists, the vast majority of whom work in public and hospital-based clinics. All patients who are to be included in this study are registered in SWIBREG (Ludvigsson et al., 2019). The linkage of this registry to other relevant nationwide registers enables monitoring of existing IBD therapies, as they are used in clinical practice.

By 2020, the SWIBREG database covered approximately 26000 patients with UC (Myrelid et al., 2021). Although the coverage is not complete, the coverage of moderate to severe UC in SWIBREG was 80-90% in 2020 and tended to be patchy (i.e. no or very poor coverage in some centers and close to complete coverage in most).

For more details on SWIBREG, see Section 8.4.3.

8.2.2. Inclusion Criteria

Across all 3 registries, adult patients (≥18 years) of any sex with UC that are enrolled in 1 of the 3 IBD registries after 10 March 2023 and during the observational period (complying with the register's requirements for inclusion including patient consent) and initiated on filgotinib after 10 March 2023. Initiation is defined as either no prior filgotinib use or prior use that was discontinued before 10 March 2023 (thus, patients who are non-naïve to filgotinib can be included).

There are no restrictions on patient inclusion in terms of either historical data or minimum amount of follow-up.

8.2.3. Exclusion Criteria

Patients who started filgotinib prior to the EC decision date without discontinuation until 10 March 2023 (= prevalent filgotinib users after the EC decision date) will be excluded.

8.2.4. Index Date, Follow-up

The index date (= start of follow-up) in each registry will be the date a patient starts UC treatment with filgotinib (i.e. the date of first identification of filgotinib exposure in the registry) after the EC decision date. The patient's total 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.

8.3. Variables

For a detailed list of variables of interest and availability by registry, see Annex 3 – Table 5.

8.3.1. Patient Baseline Characteristics

Baseline variables are collected at the 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. Baseline variables will include (as per availability by each registry):

- Age (at baseline)
- Sex
- Body mass index (BMI)
- Long-time smoking (for >10 years (Kristensen et al., 2023) (either current or past smoking)
- Date of UC diagnosis

- Severity of UC (for details, see Annex 3 – Table 5)
- Renal impairment (for details, see Annex 3 – Table 5)
- Hepatic impairment
- Type and number of previous UC treatments prior to filgotinib initiation
- Date of filgotinib initiation
- Initial filgotinib dose
- Diagnosis of active TB at index date
  - Date of diagnosis
- Active serious infection at index date
  - Date of diagnosis
- Current pregnancy (at index date)
  - Start of pregnancy
- Age ≥65 (at index date)
- History of atherosclerotic CVD (angina, coronary heart disease, myocardial infarction, congestive heart failure, stroke, peripheral arterial disease)
- Other CV risk factors (diabetes mellitus, hypertension, obesity/BMI ≥30 kg/m^2)
- Current malignancy
- History of malignancy
- Concomitant use of other immunosuppressants
- Diagnosis of viral hepatitis
  - Date of diagnosis
- Diagnosis of herpes zoster
  - Date of diagnosis
- Screening for viral hepatitis
  - Date of screening
- Laboratory measurements (measurement within ±1 month of filgotinib index date, or any time during follow-up)
  - absolute neutrophil count (ANC)
  - absolute lymphocyte count (ALC)
  - hemoglobin (Hb)
- Use of live-attenuated vaccines
- History of VTE
- Recent surgery (i.e. surgery within 1 month (Singh et al., 2023) prior to the index date or at any time during follow-up; see also Annex 3 – Table 5)
- Reduced mobility (for details, see Annex 3 – Table 5)
- Recent hospitalization (hospitalization within 1 month prior to the index date or at any time during follow-up; see also Annex 3 – Table 5)
- History of blood clotting disorders
- Concomitant use of combined hormonal contraceptives
- Concomitant use of hormone replacement therapy

8.3.2. Follow-up Variables

Follow-up variables assessed during filgotinib treatment will include (as per availability by each registry):

- Filgotinib maintenance dose and average daily dose
- Diagnosis of TB
  - Date of diagnosis
- Serious acute infection
  - Date of diagnosis
- Diagnosis of viral hepatitis
  - Date of diagnosis
- Diagnosis of herpes zoster
  - Date of diagnosis
- Pregnancy
  - Start of pregnancy
- Use of live-attenuated vaccines
- Laboratory monitoring of lipids (total cholesterol, high- and low-density lipoproteins [HDL, LDL], triglycerides) around 12 weeks after initiation of filgotinib treatment and thereafter
- Laboratory measurements (any time during follow-up)
  - ANC
  - ALC
  - Hb
- VTE event
  - Date of VTE diagnosis

8.3.3. Exposure Definition

8.3.3.1. ENEIDA (ES)

Exposure to the drugs of interest is recorded in specific predefined fields and includes items such as the specific drug, its dose, and the dates of start and end of prescription. The definition of exposure assumes that if the drug is recorded in ENEIDA, it is being used by the patient as instructed (a common assumption in observational drug utilization research).

8.3.3.2. ICC (NL)

In ICC exposure to the drugs of interest is recorded in specific predefined fields and includes items such as the specific drug, its dose, and the date of start of prescription. In the case the patient stops the drug, this will be recorded as well. The definition of exposure assumes that between the start and the stop date the drug is being used by the patient as instructed.

8.3.3.3. SWIBREG (SWE)

Drug exposures for a small molecule such as filgotinib is captured in the Prescribed Drug Register ([PDR] i.e. all dispensed prescriptions of the drug). A dispensing will be assumed to last for 180 days, after which a lack of a new dispensed prescription will be counted as a treatment hiatus.

8.4. Data Sources

The study will include information from 3 IBD registries described in more detail below.

8.4.1. ENEIDA (ES)

8.4.1.1. Study Main Data Source: the ENEIDA Registry

ENEIDA is a large, prospectively maintained registry of patients with IBD in Spain established in 2005 (Zabana et al., 2020). It is conducted under the auspices of a national scientific society devoted to the study of IBD (the Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa [Spanish Working Group on Crohn's disease and Ulcerative Colitis] GETECCU). Data in the ENEIDA registry come from a network of more than 90 academic and community gastroenterology practices across Spain that have an interest in IBD. As of February 2023, the registry's entire census of patients with UC was 37865, of which >30000 were on active follow-up. Participation in the registry is voluntary for both physicians and patients, and physicians who contribute data to ENEIDA receive no payment for this registry work. The ENEIDA registry is stored in a password-protected MySQL database that is maintained in a secure server facility and managed by dedicated data managers. The investigator or a qualified designee is responsible for verifying the accuracy of patient data as data are entered into the ENEIDA registry.

Participating sites enter data into an electronic case report form (eCRF), which is immediately uploaded in the central ENEIDA registry. Automated data in ENEIDA comprise a predefined set of clinical variables. The registry mandates completion of a limited number of fields on the eCRF, while completion of other fields is optional.

The general organization of data sources, research team, and the flow of information for the study is presented in Figure 1.

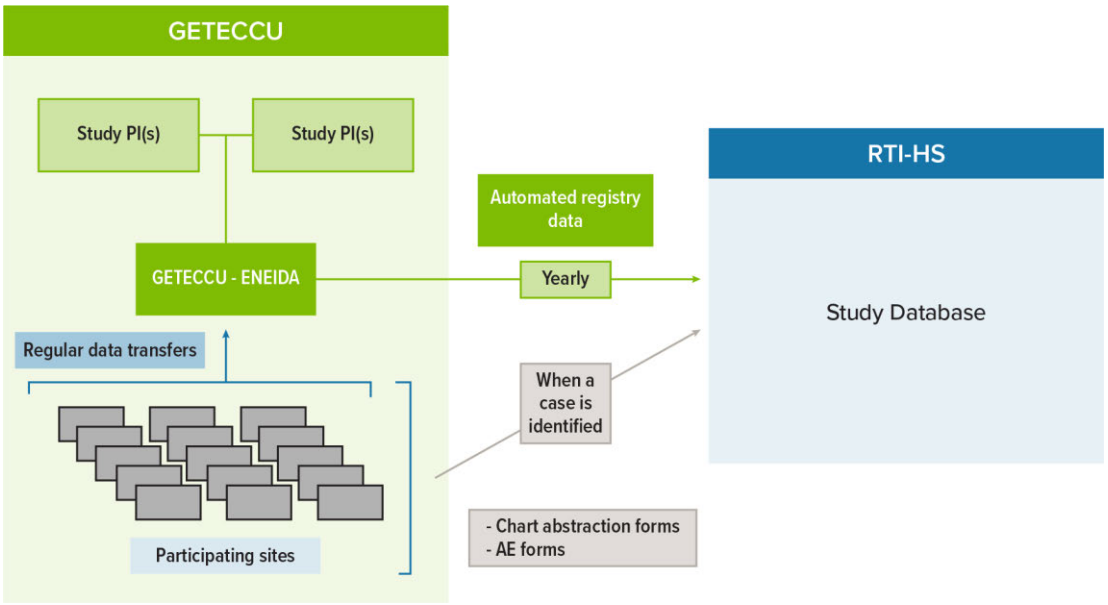

Figure 1 Organization and Flow of Study Data for ENEIDA

AE = adverse event; ENEIDA = National Study on Inflammatory Bowel Disease Genetic and Environmental Determinants; GETECCU = Spanish Working Group on Crohn's disease and Ulcerative Colitis; PI = principal investigator; RTI-HS = RTI Health Solutions.

8.4.1.2. List of Critical Variables and Calculation of Variable Completeness

ENEIDA sites are expected to record a set of critical variables for each registered patient. On a monthly basis, ENEIDA assesses the completeness of data for each contributing site for all registry patients, not just the patients seen in the clinic that month. Sites with low data completion are asked, but not compelled, to be more thorough.

The critical variables are grouped into the following categories:

1. Demographic data: date of birth, sex, date of inclusion in the registry, date of the last visit;
2. Clinical data: date of the first diagnosis of UC, current diagnosis (in case the IBD diagnosis changed since presentation), and disease location (at least if on a colonic segment);
3. Immunosuppressive therapy (yes or no, and at least 1 drug must be included if answer is "yes");
4. Biologic/advanced therapy (yes or no, and at least 1 drug must be included if answer is "yes");
5. Surgical treatment (yes or no, and at least 1 type of surgery must be included if answer is "yes").

Details of variables to be collected in ENEIDA can be found in Annex 3 – Table 5.

Calculations of percentage of data completeness include all patients registered within a site, except for sections on details of treatments (i.e. 3, 4, and 5 from the list above) that refer only to patients who received the corresponding therapies. Note that if a single critical variable in a specific section is missing, the entire section is considered to be incomplete. Each site then receives scores for completeness for each section of critical data.

Contributing sites are judged to be of research quality based on the proportion of "complete patients" from that center, i.e. the proportion of patients who have all the predefined "critical variables" completed. To define a center as a "research-quality center" an ad hoc proportion of complete patients (e.g. 95%, 90%, 85%) is selected as the threshold.

Overall, as of June 2022, 55 sites across Spain could be considered of research quality in the ENEIDA registry, based on the definition above and a threshold of 90% completeness of critical variables. Among these, 28 sites had enrolled >1,000 patients each in the ENEIDA registry, representing 78% of patients with UC in the registry.

8.4.1.3. Study Complementary Data Source: Medical Chart Abstraction

The information collected in the ENEIDA registry can be supplemented by the participation of clinical investigators at individual sites in studies where additional information is collected via electronic questionnaires. These questionnaires may collect information on variables that are not recorded in the ENEIDA registry or for which a large number of missing values is expected. Questionnaires can also be used to validate study endpoints and exposure to the drugs of interest that are identified in the ENEIDA automated registry via comparison with patient EMRs.

For the present study, a specific informed consent (IC) of patients will be required to access their EMRs (see also Section 9.3.1) since most of the questions of interest of this PASS fall outside the scope of the information collected by ENEIDA.

8.4.2. ICC (NL)

The ICC is a Dutch IBD research organization, which facilitates, coordinates, and conducts collaborative collection of data and biomaterials as well as IBD studies in the Netherlands. It has established a web-based observational, multicenter registry (the "ICC Registry") where patients with an established diagnosis of IBD (both, CD, and UC) are eligible. The study population in the registry includes all patients with IBD 16 years or older who start novel registered drugs in the Netherlands for IBD in routine care. Collected data will consist of routine care data only.

Approximately 20 centers, specialized in IBD will participate in this project, each treating roughly 30 patients with novel IBD medication in academic centers and 10 patients in district hospitals a year. All patients using filgotinib in the participating centers from 2022 onwards will be included in a prospective approach. Furthermore, the ICC drug surveillance program is divided into 2 parts: a retrospective part, from January 2014 until February 2018, and a prospective part starting in March 2018. All information will be stored for 15 years.

No additional interventions besides standard patient care are required for this study and therefore there is no additional burden or risk for patients participating in this study. The scheme set-up to standardize follow-up in participating hospitals is adapted from current guidelines and common practice. Clinical, biochemical, and adverse event (AE) data will be extracted from the patient files. All patient data is stored coded and for the retrospective part it is anonymous in the registry system MEMIC (Center for data and information management at the Faculty of Health, Medicine and Life Sciences of Maastricht University; see also Section 8.6.2). ICC aims to perform an

observational, coded registry without extra interventions to obtain data on the effectiveness in a standard patient-care setting.

8.4.2.1. Prospective Data Collection

When the treating physician has an indication to start the studied medication, the eligibility of the patient will be assessed (IBD diagnosis and >16 years of age). When an eligible patient is identified, a patient information form will be distributed, and IC obtained. The treating physician or IBD nurse from the participating center fills out patient characteristics (gender, year of birth, disease information) in the new patient eCRF (software.memic.unimaas.nl) and a code is created which will be used from here on after.

8.4.2.2. Retrospective Data Collection

Patients who started in standard care with the studied medication and finished follow-up will retrospectively and anonymously be registered in the ICC registry. Therefore, we will not ask for a patient's IC.

8.4.2.3. Pseudonymization

Each participant is assigned a unique code, consisting of a number for each center (e.g. 01 for Maastricht University Medical Center) and a 5-digit sequence number (00001 etc.): 01.00001. This code will be used for all study-related documents and materials. The participant's identity cannot be traced directly via this code. Only the local principal investigator and local coordinating researcher will have access to the local source file, in which the unique code is linked to the personal data such as name and date of birth. This file will be kept in a secure site on the hospital/institutions network and access to this file will be restricted to the clinicians participating in the study at this local center.

8.4.2.4. Standardized Treatment Protocol

The following follow-up protocol is based on current standard of care. On the day of initiating therapy, the Week 0 visit will be filled out. The next visits reflect the minimum acquired visits in routine care and are scheduled on Week 12, Week 24, Week 52, and once yearly up to 10 years after initiation of treatment. If a patient or physician decides to discontinue the medication, the medication discontinuation form will be filled out and further registration is discontinued. All patients receive standard care and no additional questions, blood samples, interventions, questionnaires, or other activities have to be performed.

If a patient discontinues the medication and initiates another treatment that is included in the ICC Registry, the follow-up is again at Week 12, 24, 52, and 1 visit yearly.

8.4.2.4.1. Week 0 (Baseline)

Clinical data on demographics, date of diagnosis, IBD phenotype and phenotype history, location of previous IBD surgery, medical history, IBD medication history, and smoking status will be collected. Furthermore, the current clinical disease activity (Harvey-Bradshaw Index [HBI]/Simple Clinical Colitis Activity Index [SCCAI]), biochemical data (Hb, thrombocytes,

leucocytes, alanine aminotransferase [ALT], alkaline phosphatase, C-reactive protein [CRP], creatinine, fecal calprotectin), current IBD medication, and, if applicable, radiologic, and endoscopic information will be collected.

8.4.2.4.2. Follow-up Visits (Week 12, 24, 52, Year 2, 3, 4, 5, 6, 7, 8, 9, 10)

During follow-up visits, the following information is collected: current clinical disease activity (HBI/SCCAI), biochemical data (Hb, thrombocytes, leucocytes, ALT, alkaline phosphatase, CRP, creatinine, fecal calprotectin), current IBD medication, complications (surgery, hospitalization), AEs (events related to medication and infections), and, if applicable, radiologic and endoscopic information.

Details of variables to be collected in ICC can be found in Annex 3 – Table 5.

8.4.3. SWIBREG (SWE)

Baseline and follow-up data, including patient demographics, disease characteristics, and treatment will be based on data from SWIBREG and the Swedish Patient and Prescribed Drug Registers. SWIBREG data will be augmented with linkages to the Swedish Cancer, Contagious Diseases, Medical Birth, Causes of Death, and Total Population Registers.

Details of variables to be collected in SWIBREG can be found in Annex 3 – Table 5.

8.4.3.1. SWIBREG (Main Data Source)

The Swedish Quality Register for patients with IBD (SWIBREG), including UC, is a structured collection of personal data that was initiated to systematically and continuously develop and safeguard quality of IBD care in Sweden (Ludvigsson et al., 2019). In SWIBREG, individual-level data have been collected from most Swedish IBD caregivers since 2005. The positive predictive value for a UC diagnosis in SWIBREG is very high (96% [95% confidence interval [CI]: 89-99]) (Jakobsson et al., 2017).

SWIBREG includes data on conventional therapies, biological treatment, surgeries, smoking, disease activity, patient-reported outcome measures, and patient-experienced measures. Although SWIBREG does not have a national coverage similar to National Patient Register (NPR) or Prescribed Drug Register (PDR), the 2 common sources of data for identifying patients with IBD in Sweden, its data allows for analysis of safety of IBD treatments over a relatively long follow-up period. Although safety events are not routinely collected in SWIBREG, data linkage to other nationwide healthcare registers (NPR, cancer register, cause of death register, contagious disease register, medical birth register, and the total population register) enables capturing all censoring events and safety endpoints of interest. Additionally, the PDR allows for confirmation of dispensed prescriptions (Bröms et al., 2021). In addition to data on safety outcomes and baseline comorbidities or disease history, SWIBREG is also the source of patients with UC naive to advanced therapies/immunomodulators/immunosuppressants agents.

8.4.3.2. National Patient Register and Prescribed Drug Register

The NPR provides information on all hospitalized (inpatient treated) patients (Ludvigsson et al., 2011), and all visits to nonprimary outpatient care (such as a visit to a gastroenterologist). Diagnoses are assigned by the physician, as well as date of discharge and discharging hospital for inpatient care, and hospital department. Diagnoses are coded according to the International Classification of Diseases (ICD), with version 8 used until 1986, version 9 from 1987 to 1996, and ICD10 since 1997. Due to routine validation and acquisition processes, data on hospital visits become available for research the earliest during the next calendar year. The PDR provides all filled prescriptions in Sweden from 1 July 2005, and may be used to aid correct classification of patients by their history of retrieved IBD therapies, or to define subcohorts based on treatment switches (Wettermark et al., 2007). A recent validation study has indicated that the coverage of the infusion drugs in the PDR is not optimal (Bröms et al., 2021).

8.4.3.3. The Contagious Disease Register

The Swedish Contagious Disease Register (SmiNet), established in 1971, provides events reported according to the Communicable Diseases Act and the Communicable Diseases Ordinance on diseases that have mandatory reporting in Sweden (e.g. TB).

8.4.3.4. The Swedish Cancer Register

The Swedish Cancer Register was established in 1958 and provides data on date of cancer (and some selected precancers) onset, and type of cancer according to the ICD classification and morphology/histology (Barlow et al., 2009). About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi-automated, resulting in an estimated coverage greater than 95%.

8.4.3.5. 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 collected 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 ICD10 since 1997 onwards (Cnattingius et al., 1990).

8.4.3.6. 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. Although the register was started in 1952, the data are considered complete since 1961 (de Faire et al., 1976).

8.4.3.7. The Total Population Register

The Total Population Register lists data on residency at a given point in time since it was founded in 1961, and dates of emigration/immigration for all subjects ever resident in Sweden since 1961. This register thus provides information on censoring (death and emigration) of patients (Ludvigsson et al., 2016).

8.5. Study Size

This is a descriptive study without prespecified hypotheses. The goal is to obtain data on up to 500 eligible patients with UC initiating filgotinib during the observational period (per registry) and thus the study size will be dictated by the number of filgotinib patients identified in the participating registries. For illustrative purposes, by applying the rule-of-3 (Hanley & Lippman-Hand, 1983) and assuming an underlying proportion e.g. of a contraindication of 1%, implies that the 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 3).

Table 3 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 observed proportion of patients at high risk, for example MACE, is 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% CI of 6.6% to 13.4% (Altman, 1999). Other scenarios of precision are provided in Table 4 and Figure 2.

Table 4 Standard Error by Study Size and Underlying Proportion

	Study Size			
Proportion*	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. Calculations are based on a normal distribution assumption for the proportion

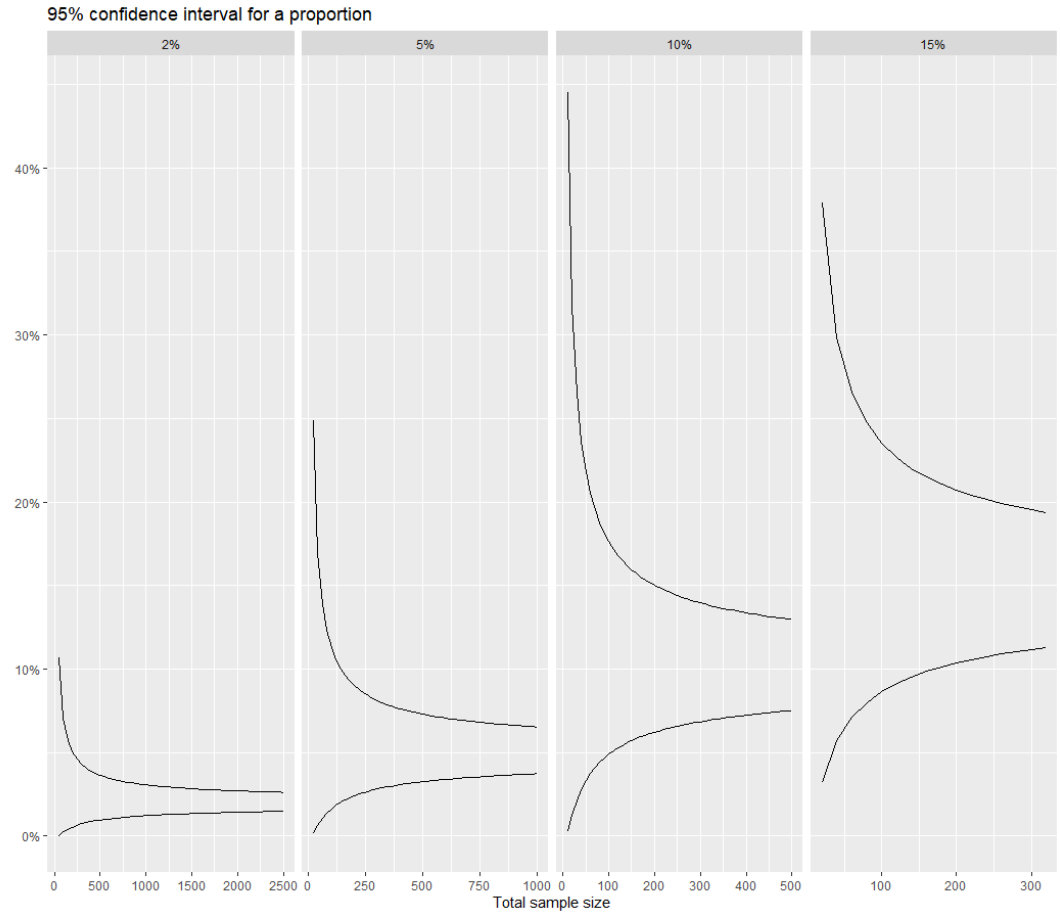

Figure 2 Estimated 95% Confidence Interval by Study Size and Underlying Proportion (Assuming a Binomial Distribution)

8.6. Data Management

8.6.1. ENEIDA (ES)

This study will involve analysis of secondary data from the ENEIDA registry, as described in Section 8.4. The automated data are maintained and managed by the ENEIDA registry in a password-protected MySQL database, which is maintained on a server in a secure facility. The investigator or qualified designee is responsible for verifying the accuracy of patient data as it is entered into the ENEIDA registry. All analyses will be conducted using SAS software.

This study involves chart review for all patients exposed to filgotinib identified in the automated data. Linkage between the automated record and the patient record will be based on the patient identification number and clinical site identifier.

Data will be accessed by Research Triangle Institute Health Solutions (RTI-HS) according to ENEIDA's standard practice. RTI-HS will log on to the ENEIDA secure server, download the data files, and store the data in a secure server in Barcelona with backups in the EU. Only selected RTI-HS personnel in Barcelona will have access to the data. Once the data are received,

RTI-HS will develop a data dictionary using SAS PROC CONTENTS. The data dictionary will document any data transformations applied to the received data sets to create the analytical datasets. The data dictionary will include variable names, formats, and any SAS code used to create derived variables from raw variables.

The transfers of data from ENEIDA may include data for patients who do not qualify for the analytic purposes of the present study. However, these data may be used to determine whether the analytic database is representative of the ENEIDA registry data in its totality. All data received from the registry will be covered by the IC signed by all patients at enrolment in ENEIDA. Chart abstraction will require patients to sign a study-specific IC to be able to obtain information of variables that are not part of the ENEIDA registry scope (see also Section 9.3.1). Data not used for the analysis will be filtered out at RTI-HS. Only data essential to the planned analyses will be retained in the analytic database.

8.6.2. ICC (NL)

The data management program of choice will be designed, built, provided, and supported by MEMIC, an information and communication technology-company affiliated to Maastricht University, Maastricht, the Netherlands. The database is designed for adequate and safe data recording, and MEMIC ensures that the strict rules concerning anonymity of medical data, access to the data and storage of the medical data are followed. The database is linked to a logistic program (called Logis) which will determine the moments of follow-up. Physicians will get an alert from the program when a new follow-up moment has to be scheduled for a patient.

The follow-up protocol is based on current standard of care (see Section 8.4.2). Visits are at initiation of therapy, at Week 12, 24, 52, 104, and once yearly thereafter. If patients stop therapy, a discontinuation visit form is filled in. A reminder for every visit is sent by email to the treating physician or nurse 3 weeks before the scheduled visit date.

Each participant is assigned a unique code, consisting of a number for each center and a 5-digit sequence number. This code will be used for all study-related documents and materials. The participant's identity cannot be traced directly via this code. Only the local principal investigator and local coordinating researcher will have access to the local source file, in which the unique code is linked to the personal data such as name and date of birth. This file will be kept in a secure site on the hospital/institutions network and access to this file will be restricted to the clinicians participating in the study at this local center.

All analyses will be conducted using the IBM SPSS Statistics for Windows, version 24.0 or higher (IBM, Armonk, NY).

8.6.3. SWIBREG (SWE)

This study analyses secondary data available through SWIBREG and several other nationwide registers. Researchers from the Karolinska Institute (KI) are responsible for the data management of this study. As previously described (Section 8.4.3), 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 pseudonymized data for research purposes. The data obtained for this study will reside on restricted, double backed-up servers at the Clinical Epidemiology Division at the Karolinska University Hospital Campus. Trained statistician/epidemiologist staff will perform data 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. According to the Swedish law, the data, programs, and documents related to study reports will be maintained for a minimum of 10 years.

The data retrieval and linkage include the following steps:

1. At end of study follow-up (or data cut-off point for interim reports), data will be ordered from SWIBREG and the Swedish Board of Health and Welfare.
2. The data provider of SWIBREG (Health Solutions) will export quality register data to the Board of Health and Welfare.
3. The Board of Health and Welfare will create a study cohort, consisting of all included patients and send the list of their personal identification numbers to Statistics Sweden.
4. A list of all study participants will be sent back to the Board of Health and Welfare and there the study population will be linked to all the health registers.
5. A pseudonymized dataset consisting of all patients with UC will be sent to the study researchers at KI. The key to the dataset will be kept at the Board of Health and Welfare, which makes updates to the dataset possible in the future but identification of individual patients impossible for the researchers.

At KI standard statistical software including SAS, STATA, and R is used.

8.7. Data Analysis

Detailed methodology for the analyses of data included in this study will be documented in a common and harmonized statistical analysis plan (SAP), which will be created by the study coordinating center with input from investigators from the 3 registries, dated, filed, and archived by the MAH. Data analysis summarized in the protocol may be modified in the SAP to reflect usage of the most up-to-date methodology used by the different registries.

Data will be summarized using univariable descriptive statistical methods. Categorical outcome variables will be summarized by number and percentage of patients in each categorical definition including 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).

Follow-up

Among women starting filgotinib, the number and proportion who become pregnant during follow-up will be reported. Similarly, the number and proportion of patients who have a new

diagnosis of TB during follow-up, a serious acute infection, a diagnosis of viral hepatitis, concomitant treatment with other immunosuppressants, or who are administered a live attenuated vaccine will be reported. In patients with TB, or a serious infection identified during follow-up, it will be assessed whether treatment was stopped or interrupted after the diagnosis. The proportion of patients who have a test for lipids at around 12 weeks since initiation of filgotinib will be reported.

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

Assessment of the filgotinib maintenance dose during follow-up will also be done in the subgroup of patients at high risk of MACE, VTE, or malignancy. In addition, the average daily dose during the maintenance period and the duration of use during the follow-up period will be reported.

8.7.1. Missing Values

8.7.1.1. ENEIDA (ES)

No imputation for missing data is done at ENEIDA. In most instances, absence of information for a predefined variable is taken as evidence of absence of the condition, treatment, etc. coded by the variable. For variables with true missingness such as age or sex, missing values will be quantified and accounted for as described in the SAP.

8.7.1.2. ICC (NL)

If data are missing, patients are calculated as nonresponders. However, since there is prospective follow-up and centers are alerted if a visit is in the near future, missing data is limited. ICC does not use imputation for missing values.

8.7.1.3. SWIBREG (SWE)

Missing baseline values are expected to be rare. For this reason, imputation for missing data points will not be performed in this study. However, variables with missing data will be described.

8.8. Quality Control

8.8.1. ENEIDA (ES)

During the preparation of the analytic file for this study, quality control measures will include checks for legitimate values for each categorical variable and logic checks for dates. There are no plans to systematically clean the ENEIDA data via queries after data are received.

The chart abstraction data will be checked for content by edit checks programmed into the PDF form, as stated in the edit check specifications document that will be prepared. In addition, sites will be queried for nonsensical data (e.g. dates that appear to be in the wrong format).

8.8.2. ICC (NL)

Data are filled in at the participating center by the treating physician or nurse. The ICC fellow regularly visits the participating centers and checks the data at random or in more detail if necessary. There are quality checks build in the eCRF (e.g. a maximum amount of digits for CRP). After receiving the SPSS file by MEMIC, data is checked for legitimate values for each variable and logic checks for dates.

8.8.3. SWIBREG (SWE)

This study uses data existing within SWIBREG and several national registers in Sweden including NPR and PDR. Data management will include cleaning of data to remove illogical values, derive study variables, and structure the data to perform the required statistical analyses. All data management will be conducted on servers at KI using standard statistical software including SAS, STATA, and R.

The quality control of data and statistical programs developed will include:

- Adherence to requirements and specifications outlined in the SAP. Any deviations will be reported
- Review of individual data linkage across registers
- Review of log files (errors, outliers, warnings, missing values, and notes)
- Review of distributions (histogram, min-max, median, percentiles, mean, standard deviation) of continuous variables and frequencies for all possible values of discrete variables

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

8.9. Limitations of the Research Methods

This non-interventional, registry-based DUS aims to evaluate the effectiveness of the aRMMs for filgotinib prescribed for treatment of patients with UC using information collected by 3 European IBD registries. Despite the strengths of this DUS, results must be evaluated considering their limitations.

Most importantly, as per the updated filgotinib SmPC, it is recommended that e.g. in patients 65 years of age or older, or those with history of atherosclerotic CVD disease or other CV risk factors, or in patients with malignancy risk factors, filgotinib should only be used ‘if no suitable treatment alternatives are available’. Whether suitable treatment alternatives are available for a patient is an individual assessment made by the HCP together with the patient, taking into account patient characteristics and preferences. Given the nature of these assessments, a non-interventional study with secondary data use will not be able to reliably assess whether ‘no suitable treatment alternatives’ were available. This limitation is partly addressed, however, by

assessing the previous history of UC treatment prior to initiation of filgotinib and additional information such as reasons for switching prior UC treatment(s).

The quality of the registry data is not comparable to that of clinical trials due to less stringent data quality monitoring. 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 DUS examines medical history which may not be available in the clinical records and thus relies on memory. In addition, there may be heterogeneity in data quality within centers, and between countries. This could inflate (but also mask) genuine differences between the results from the registries.

Furthermore, not all information that is relevant in the context of this DUS may be captured by all registries. For instance, in the context of skin malignancies (NMSC), none of the registries systemically records information on periodic skin examination. Therefore, this cannot be reliably followed or measured in any of the three registries used in this DUS. Moreover, not all registries capture the same information, nor is the process of data capturing the same. While e.g. in SWIBREG – due to data linkage to various other Swedish data sources and registries – the vast majority of variables will be available, in ENEIDA information on many variables will need to be extracted from EMRs.

The analyses of this DUS will be restricted to the period after the EC decision date on the JAKi Article 20 procedure (10 March 2023), and therefore not include filgotinib data of the pre-referral period. The rationale for this is that the number of patients identified in the registries exposed to filgotinib in the pre-referral period, i.e. between the filgotinib EU approval date (Netherlands: 12-Nov-2021; Spain: 01-May-2023 [= date of reimbursement approval of filgotinib in Spain on a national level]; Sweden: 12-Nov-2021) and the EC decision date is very limited (ICC: n=54; ENEIDA: n=19; SWIBREG n=44).

Any non-interventional study can suffer from bias, specifically, selection or information bias. However, this study aims to capture up to 500 consecutive patients per registry initiating filgotinib in the observational period. Therefore, this study will reflect the clinical practice and characteristics of these patients.

8.10. Other Aspects

8.10.1. Sponsor's and Investigator's Responsibilities

The MAH reserves the right to fully terminate this non-interventional PASS at any time ("Full Termination"), while each registry (i.e. ENEIDA, ICC, and SWIBREG) 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, each registry and other participating parties) 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.

The name and address of each third-party vendor (e.g. scientific service provider [e.g. RTI-HS]) used in this study and the sponsor's study team members will be maintained in the investigator's and sponsor's files as appropriate.

Prior to study start, this protocol together with all relevant documentation needs to be submitted to the respective regulatory authorities and IEC/IRBs for review and approval in compliance with current regulations before the study can start.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

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

9.2. Institutional Review Board or Independent Ethics Committee Review

9.2.1. ENEIDA (ES)

The study protocol will be reviewed and endorsed by GETECCU (the scientific society maintaining the ENEIDA registry) and the study's reference ethics committee (to be determined), In addition, the ethics committee of each hospital participating in the chart review component of the study will also review and approve the protocol, commensurate with local law. The study will be registered in the Spanish Registry for Clinical Studies.

9.2.2. ICC (NL)

The registry study protocol was reviewed and approved by the ICC (the scientific society Initiative on Crohn and Colitis), Commissie Mensgebonden Onderzoek (CMO) Radboudumc and ethics committees of the participating centers.

9.2.3. SWIBREG (SWE)

This study will make secondary use of existing data collected by SWIBREG and other national Swedish registers. The data are at individual level, pseudonymized, and stored on secure servers at KI. The SWIBREG register linkage database does not contain any identifying information from patients (for example, name), except for a unique number assigned for the purpose of linking files. This comparative safety study has been approved by the Regional Ethical Review Board in Stockholm (2022-01-14/2021-06209-01). A renewed ethical approval will be sought as needed for the duration of the study.

9.3. Informed Consent

9.3.1. ENEIDA (ES)

This non-interventional study will involve no administration of any therapeutic agent according to the study protocol; patients in ENEIDA are treated in the setting of usual clinical care. Patients whose data are included in ENEIDA previously consented to have their health information included in this database.

For the current study, some of the variables of interest extend beyond the field of UC and are not routinely collected in ENEIDA. As a consequence, a new IC will need to be obtained for this PASS for all patients that participate in the chart abstraction component of the study. If necessary, because of low enrolment in the chart abstraction component, patients for whom an IC cannot be obtained may still participate in the study addressing only those objectives that can be assessed using data collected in the registry.

9.3.2. ICC (NL)

When an eligible patient is identified for the prospective part, patient information form will be distributed, and IC obtained. For the retrospective part, no IC is required.

9.3.3. SWIBREG (SWE)

The SWIBREG register obtains IC when enrolling patients. This project does not need collecting additional ICs because available (secondary) data will be used. Furthermore, this study will make secondary use of existing data collected by SWIBREG that are pseudonymized and contain no identifiable patient information. In accordance with Swedish law, non-interventional studies of register-based data (including “quality of care” registers such as SWIBREG) do not usually require IC 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.

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, registry-based PASS making secondary use of existing registry data within the ENEIDA, ICC, and SWIBREG registers, where individual patient data are de-identified within safety data. Therefore, the MAH will not collect or report individual case safety reports in an expedited fashion. All the safety data are collected per registries standard procedures.

Data from this study will be presented in aggregate in the interim report and the final study report and in the periodic benefit-risk evaluation reports/periodic safety update reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Study Report and Publications

An interim report with 2 years of data will be submitted no later than 9 months after end of data collection. The final study report with 4 years of data will be provided within 12 months after the end of data collection and will be included in risk management plan updates.
Note: end of data collection (i.e. when the minimum analytical dataset to perform the statistical analyses leading to the results for the primary objective(s) is completely available) is different for individual registries and includes e.g. the time needed to perform medical chart abstraction, data linkage, data cleaning etc. Therefore, there may be a considerable time lag between reaching the end of the observational period and the end of data collection.

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

In addition, results of the study may be published in a scientific journal.

12. REFERENCES

Altman, D. G. (1999). *Practical statistics for medical research*. Chapman & Hall/CRC.

Ananthakrishnan, A. N. (2015). Epidemiology and risk factors for IBD. *Nat. Rev. Gastroenterol. Hepatol.*, *12*(4), 205–217. https://doi.org/10.1038/nrgastro.2015.34

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

Bröms, G., Söderling, J., Sachs, M. C., Halfvarson, J., SWIBREG study group, Myrelid, P., Ludvigsson, J. F., Everhov, Å. H., & Olén, O. (2021). Capturing biologic treatment for IBD in the Swedish Prescribed Drug Register and the Swedish National Patient Register - a validation study. *Scand. J. Gastroenterol.*, *56*(4), 410–421. https://doi.org/10.1080/00365521.2021.1884894

Brunet, E., Roig-Ramos, C., Vela, E., Clèries, M., Melcarne, L., Villòria, A., Pontes, C., & Calvet, X. (2018). Prevalence, incidence and mortality of inflammatory bowel disease in Catalonia. A population-based analysis. *Ann. Med.*, *50*(7), 613–619. https://doi.org/10.1080/07853890.2018.1523550

Burisch, J., Pedersen, N., Čuković-Čavka, S., Brinar, M., Kaimakliotis, I., Duricova, D., Shonová, O., Vind, I., Avnstrøm, S., Thorsgaard, N., Andersen, V., Krabbe, S., Dahlerup, J. F., Salupere, R., Nielsen, K. R., Olsen, J., Manninen, P., Collin, P., Tsianos, E. V., Katsanos, K. H., Ladefoged, K., Lakatos, L., Björnsson, E., Ragnarsson, G., Bailey, Y., Odes, S., Schwartz, D., Martinato, M., Lupinacci, G., Milla, M., De Padova, A., D'Incà, R., Beltrami, M., Kupcinskas, L., Kiudelis, G., Turcan, S., Tighineanu, O., Mihu, I., Magro, F., Barros, L. F., Goldis, A., Lazar, D., Belousova, E., Nikulina, I., Hernandez, V., Martinez-Ares, D., Almer, S., Zhulina, Y., Halfvarson, J., Arebi, N., Sebastian, S., Lakatos, P. L., Langholz, E., Munkholm, P., & EpiCom-group. (2014). East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. *Gut*, *63*(4), 588–597. https://doi.org/10.1136/gutjnl-2013-304636

Burisch, Johan, Lophaven, S., Munkholm, P., & Langholz, E. (2022). Surgery, cancer and mortality among patients with ulcerative colitis diagnosed 1962-1987 and followed until 2017 in a Danish population-based inception cohort. *Aliment. Pharmacol. Ther.*, *55*(3), 339–349. https://doi.org/10.1111/apt.16677

Chaparro, M., Garre, A., Núñez Ortiz, A., Diz-Lois Palomares, M. T., Rodríguez, C., Riestra, S., Vela, M., Benítez, J. M., Fernández Salgado, E., Sánchez Rodríguez, E., Hernández, V., Ferreiro-Iglesias, R., Ponferrada Díaz, Á., Barrio, J., Huguet, J. M., Sicilia, B., Martín-Arranz, M. D., Calvet, X., Ginard, D., Alonso-Abreu, I., Fernández-Salazar, L., Varela Trastoy, P., Rivero, M., Vera-Mendoza, I., Vega, P., Navarro, P., Sierra, M., Cabriada, J. L., Aguas, M., Vicente, R., Navarro-Llavat, M., Echarri, A., Gomollón, F., Guerra Del Río, E., Piñero, C., Casanova, M. J., Spicakova, K., Ortiz de Zarate, J., Torrella Cortés, E., Gutiérrez, A., Alonso-Galán, H., Hernández-Martínez, Á., Marrero, J. M., Lorente Poyatos, R., Calafat, M., Martí Romero, L.,

Robledo, P., Bosch, O., Jiménez, N., Esteve Comas, M., Duque, J. M., Fuentes Coronel, A. M., Josefa Sampedro, M., Sesé Abizanda, E., Herreros Martínez, B., Pozzati, L., Fernández Rosáenz, H., Crespo Suarez, B., López Serrano, P., Lucendo, A. J., Muñoz Vicente, M., Bermejo, F., Ramírez Palanca, J. J., Menacho, M., Carmona, A., Camargo, R., Torra Alsina, S., Maroto, N., Nerín de la Puerta, J., Castro, E., Marín-Jiménez, I., Botella, B., Sapiña, A., Cruz, N., Forcelledo, J. L. F., Bouhmidi, A., Castaño-Milla, C., Opio, V., Nicolás, I., Kutz, M., Abraldes Bechiarelli, A., Gordillo, J., Ber, Y., Torres Domínguez, Y., Novella Durán, M. T., Rodríguez Mondéjar, S., Martínez-Cerezo, F. J., Kolle, L., Sabat, M., Ledezma, C., Iyo, E., Roncero, Ó., Irisarri, R., Lluis, L., Blázquez Gómez, I., Zapata, E. M., José Alcalá, M., Martínez Pascual, C., Montealegre, M., Mata, L., Monrobel, A., Hernández Camba, A., Hernández, L., Tejada, M., Mir, A., Galve, M. L., Soler, M., Hervías, D., Gómez-Valero, J. A., Barreiro-de Acosta, M., Rodríguez-Artalejo, F., García-Esquinas, E., Gisbert, J. P., & On Behalf Of The EpidemIBD Study Group Of Geteccu, null. (2021). Incidence, Clinical Characteristics and Management of Inflammatory Bowel Disease in Spain: Large-Scale Epidemiological Study. *J. Clin. Med.*, *10*(13), 2885. https://doi.org/10.3390/jcm10132885

Chen, B., Collen, L. V., Mowat, C., Isaacs, K. L., Singh, S., Kane, S. V., Farraye, F. A., Snapper, S., Jneid, H., Lavie, C. J., & Krittanawong, C. (2022). Inflammatory Bowel Disease and Cardiovascular Diseases. *Am. J. Med.*, *135*(12), 1453–1460. https://doi.org/10.1016/j.amjmed.2022.08.012

Cnattingius, S., Ericson, A., Gunnarskog, J., & Källén, B. (1990). A quality study of a medical birth registry. *Scand. J. Soc. Med.*, *18*(2), 143–148. https://doi.org/10.1177/140349489001800209

Côté-Daigneault, J., Bessissow, T., Nicolae, M. V., Nie, R., Bitton, A., Lakatos, P. L., & Brassard, P. (2019). Herpes Zoster Incidence in Inflammatory Bowel Disease Patients: A Population-Based Study. *Inflamm. Bowel Dis.*, *25*(5), 914–918. https://doi.org/10.1093/ibd/izy311

D'Amico, F., Magro, F., Peyrin-Biroulet, L., & Danese, S. (2022). Positioning Filgotinib in the Treatment Algorithm of Moderate to Severe Ulcerative Colitis. *J. Crohns Colitis*, *16*(5), 835–844. https://doi.org/10.1093/ecco-jcc/jjab206

de Faire, U., Friberg, L., Lorich, U., & Lundman, T. (1976). A validation of cause-of-death certification in 1,156 deaths. *Acta Med. Scand.*, *200*(3), 223–228. https://doi.org/10.1111/j.0954-6820.1976.tb08223.x

de Groof, E. J., Rossen, N. G. M., van Rhijn, B. D., Karregat, E. P. M., Boonstra, K., Hageman, I., Bennebroek Evertsz, F., Kingma, P. J., Naber, A. H. J., van den Brande, J. H. M., Mallant-Hent, R. C., Mundt, M. W., D'Haens, G. R. A. M., & Ponsioen, C. Y. (2016). Burden of disease and increasing prevalence of inflammatory bowel disease in a population-based cohort in the Netherlands. *Eur. J. Gastroenterol. Hepatol.*, *28*(9), 1065–1072. https://doi.org/10.1097/MEG.0000000000000660

Dhillon, S., & Keam, S. J. (2020). Filgotinib: First Approval. *Drugs*, *80*(18), 1987–1997. https://doi.org/10.1007/s40265-020-01439-0

European Medicines Agency. (Oct 2021). Guideline on registry-based studies. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf. Accessed Jan 2022.

European Medicines Agency. (2022). *EMA starts safety review of Janus kinase inhibitors for inflammatory disorders*. Available at: https://www.ema.europa.eu/en/news/ema-starts-safety-review-janus-kinase-inhibitors-inflammatory-disorders. Accessed 29 Nov 2022.

Everhov, Å. H., Halfvarson, J., Myrelid, P., Sachs, M. C., Nordenvall, C., Söderling, J., Ekbom, A., Neovius, M., Ludvigsson, J. F., Askling, J., & Olén, O. (2018). Incidence and Treatment of Patients Diagnosed With Inflammatory Bowel Diseases at 60 Years or Older in Sweden. *Gastroenterology*, *154*(3), 518-528.e15. https://doi.org/10.1053/j.gastro.2017.10.034

Feagan, B. G., Danese, S., Loftus, E. V., Vermeire, S., Schreiber, S., Ritter, T., Fogel, R., Mehta, R., Nijhawan, S., Kempiński, R., Filip, R., Hospodarskyy, I., Seidler, U., Seibold, F., Beales, I. L. P., Kim, H. J., McNally, J., Yun, C., Zhao, S., Liu, X., Hsueh, C.-H., Tasset, C., Besuyen, R., Watanabe, M., Sandborn, W. J., Rogler, G., Hibi, T., & Peyrin-Biroulet, L. (2021). Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. *Lancet Lond. Engl.*, *397*(10292), 2372–2384. https://doi.org/10.1016/S0140-6736(21)00666-8

Feuerstein, J. D., Moss, A. C., & Farraye, F. A. (2019). Ulcerative Colitis. *Mayo Clin. Proc.*, *94*(7), 1357–1373. https://doi.org/10.1016/j.mayocp.2019.01.018

Gajendran, M., Loganathan, P., Jimenez, G., Catinella, A. P., Ng, N., Umapathy, C., Ziade, N., & Hashash, J. G. (2019). A comprehensive review and update on ulcerative colitis. *Dis.--Mon. DM*, *65*(12), 100851. https://doi.org/10.1016/j.disamonth.2019.02.004

Greuter, T., Vavricka, S., König, A. O., Beaugerie, L., Scharl, M., & Swiss IBDnet, an official working group of the Swiss Society of Gastroenterology. (2020). Malignancies in Inflammatory Bowel Disease. *Digestion*, *101 Suppl 1*, 136–145. https://doi.org/10.1159/000509544

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

Harrington, R., Al Nokhatha, S. A., & Conway, R. (2020). JAK Inhibitors in Rheumatoid Arthritis: An Evidence-Based Review on the Emerging Clinical Data. *J. Inflamm. Res.*, *13*, 519–531. https://doi.org/10.2147/JIR.S219586

Harris, C., & Cummings, J. R. F. (2021). JAK1 inhibition and inflammatory bowel disease. *Rheumatol. Oxf. Engl.*, *60*(Supple 2), ii45–ii51. https://doi.org/10.1093/rheumatology/keaa896

Irving, P. M., de Lusignan, S., Tang, D., Nijher, M., & Barrett, K. (2021). Risk of common infections in people with inflammatory bowel disease in primary care: a population-based cohort study. *BMJ Open Gastroenterol.*, *8*(1), e000573. https://doi.org/10.1136/bmjgast-2020-000573

Jakobsson, G. L., Sternegård, E., Olén, O., Myrelid, P., Ljung, R., Strid, H., Halfvarson, J., & Ludvigsson, J. F. (2017). Validating inflammatory bowel disease (IBD) in the Swedish National

Patient Register and the Swedish Quality Register for IBD (SWIBREG). *Scand. J. Gastroenterol.*, *52*(2), 216–221. https://doi.org/10.1080/00365521.2016.1246605

King, D., Reulen, R. C., Thomas, T., Chandan, J. S., Thayakaran, R., Subramanian, A., Gokhale, K., Bhala, N., Nirantharakumar, K., Adderley, N. J., & Trudgill, N. (2020). Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018. *Aliment. Pharmacol. Ther.*, *51*(10), 922–934. https://doi.org/10.1111/apt.15701

Klungel, O. H., Kurz, X., de Groot, M. C. H., Schlienger, R. G., Tcherny-Lessenot, S., Grimaldi, L., Ibáñez, L., Groenwold, R. H. H., & Reynolds, R. F. (2016). Multi-centre, multi-database studies with common protocols: lessons learnt from the IMI PROTECT project. *Pharmacoepidemiol. Drug Saf.*, *25 Suppl 1*, 156–165. https://doi.org/10.1002/pds.3968

Kristensen, L. E., Danese, S., Yndestad, A., Wang, C., Nagy, E., Modesto, I., Rivas, J., & Benda, B. (2023). Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL Surveillance. *Ann. Rheum. Dis.*, *82*(7), 901–910. https://doi.org/10.1136/ard-2022-223715

Laugesen, K., Ludvigsson, J. F., Schmidt, M., Gissler, M., Valdimarsdottir, U. A., Lunde, A., & Sørensen, H. T. (2021). Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. *Clin. Epidemiol.*, *13*, 533–554. https://doi.org/10.2147/CLEP.S314959

Lo, B., Zhao, M., Vind, I., & Burisch, J. (2021). The Risk of Extraintestinal Cancer in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis of Population-based Cohort Studies. *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.*, *19*(6), 1117-1138.e19. https://doi.org/10.1016/j.cgh.2020.08.015

Ludvigsson, J. F., Almqvist, C., Bonamy, A.-K. E., Ljung, R., Michaëlsson, K., Neovius, M., Stephansson, O., & Ye, W. (2016). Registers of the Swedish total population and their use in medical research. *Eur. J. Epidemiol.*, *31*(2), 125–136. https://doi.org/10.1007/s10654-016-0117-y

Ludvigsson, J. F., Andersson, E., Ekbom, A., Feychting, M., Kim, J.-L., Reuterwall, C., Heurgren, M., & Olausson, P. O. (2011). External review and validation of the Swedish national inpatient register. *BMC Public Health*, *11*, 450. https://doi.org/10.1186/1471-2458-11-450

Ludvigsson, J. F., Andersson, M., Bengtsson, J., Eberhardson, M., Fagerberg, U. L., Grip, O., Halfvarson, J., Hjortswang, H., Jäghult, S., Karling, P., Nordenvall, C., Olén, O., Olsson, M., Rejler, M., Strid, H., & Myrelid, P. (2019). Swedish Inflammatory Bowel Disease Register (SWIBREG) - a nationwide quality register. *Scand. J. Gastroenterol.*, *54*(9), 1089–1101. https://doi.org/10.1080/00365521.2019.1660799

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

Macaluso, F. S., Mocci, G., Orlando, A., Scondotto, S., Fantaci, G., Antonelli, A., Leone, S., Previtali, E., Cabras, F., & Cottone, M. (2019). Prevalence and incidence of inflammatory bowel disease in two Italian islands, Sicily and Sardinia: A report based on health information systems. *Dig. Liver Dis. Off. J. Ital. Soc. Gastroenterol. Ital. Assoc. Study Liver*, *51*(9), 1270–1274. https://doi.org/10.1016/j.dld.2019.05.017

Mannucci, A., D'Amico, F., El Saadi, A., Peyrin-Biroulet, L., & Danese, S. (2022). Filgotinib for moderately to severely active ulcerative colitis. *Expert Rev. Gastroenterol. Hepatol.*, *16*(10), 927–940. https://doi.org/10.1080/17474124.2022.2138857

Marín-Jiménez, I., Saro, C., Díaz, V., Acosta, M. B., Gómez-García, M., & Casbas, A. G. (2018). Epidemiology and hospital resources use in the treatment of ulcerative colitis at gastroenterology units in Spain (EPICURE study). *Drugs Context*, *7*, 212505. https://doi.org/10.7573/dic.212505

Myrelid, P., Strid, H., Ludvigsson, J. F., Bengtsson, J., Jäghult, S., Hjortswang, H., Halfvarson, J., Eberhardson, M., Rejler, M., Nordenvall, C., Björk, J., Karling, P., Olsson, M., Grip, O., Fagerberg, U. L., Olén, O., Andersson, M., Carlsson, A., & Gustavsson, K. (2021). *SWIBREG Årsrapport för 2020*. Available at: https://www.swibreg.se/wp-content/uploads/2021/09/SWIBREG_Arsrapport_for_2020.pdf. Accessed 31 Jan 2022.

Ng, S. C., Shi, H. Y., Hamidi, N., Underwood, F. E., Tang, W., Benchimol, E. I., Panaccione, R., Ghosh, S., Wu, J. C. Y., Chan, F. K. L., Sung, J. J. Y., & Kaplan, G. G. (2017). Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet Lond. Engl.*, *390*(10114), 2769–2778. https://doi.org/10.1016/S0140-6736(17)32448-0

Olén, O., Erichsen, R., Sachs, M. C., Pedersen, L., Halfvarson, J., Askling, J., Ekbom, A., Sørensen, H. T., & Ludvigsson, J. F. (2020). Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. *Lancet Lond. Engl.*, *395*(10218), 123–131. https://doi.org/10.1016/S0140-6736(19)32545-0

Román, A. L. S. (2011). Comorbidity in inflammatory bowel disease. *World J. Gastroenterol.*, *17*(22), 2723. https://doi.org/10.3748/wjg.v17.i22.2723

Shen, X., Wan, Q., Zhao, R., Wu, Y., Wang, Y., Cui, Y., Su, X., & Wu, X. (2021). Inflammatory bowel diseases and the risk of adverse health outcomes: Umbrella review of meta-analyses of observational studies. *Dig. Liver Dis.*, *53*(7), 809–816. https://doi.org/10.1016/j.dld.2021.01.018

Singh, T., Lavikainen, L. I., Halme, A. L. E., Aaltonen, R., Agarwal, A., Blanker, M. H., Bolsunovskyi, K., Cartwright, R., García-Perdomo, H., Gutschon, R., Lee, Y., Pourjamal, N., Vernooij, R. W. M., Violette, P. D., Haukka, J., Guyatt, G. H., & Tikkinen, K. A. O. (2023). Timing of symptomatic venous thromboembolism after surgery: meta-analysis. *Br. J. Surg.*, *110*(5), 553–561. https://doi.org/10.1093/bjs/znad035

Taneja, V., El-Dallal, M., Haq, Z., Tripathi, K., Systrom, H. K., Wang, L. F., Said, H., Bain, P. A., Zhou, Y., & Feuerstein, J. D. (2021). Effectiveness and Safety of Tofacitinib for Ulcerative

Colitis: Systematic Review and Meta-analysis. *J. Clin. Gastroenterol.* https://doi.org/10.1097/MCG.0000000000001608

Tosca, J., Garcia, N., Pascual, I., Bosca-Watts, M. M., Anton, R., Sanahuja, A., Mas, P., Mora, F., & Minguez, M. (2020). Clinical assessment of risk factors for infection in inflammatory bowel disease patients. *Int. J. Colorectal Dis.*, *35*(3), 491–500. https://doi.org/10.1007/s00384-019-03501-0

Ungaro, R., Mehandru, S., Allen, P. B., Peyrin-Biroulet, L., & Colombel, J.-F. (2017). Ulcerative colitis. *Lancet Lond. Engl.*, *389*(10080), 1756–1770. https://doi.org/10.1016/S0140-6736(16)32126-2

Weissman, S., Sinh, P., Mehta, T. I., Thaker, R. K., Derman, A., Heiberger, C., Qureshi, N., Amrutiya, V., Atoot, A., Dave, M., & Tabibian, J. H. (2020). Atherosclerotic cardiovascular disease in inflammatory bowel disease: The role of chronic inflammation. *World J. Gastrointest. Pathophysiol.*, *11*(5), 104–113. https://doi.org/10.4291/wjgp.v11.i5.104

Wettermark, B., Hammar, N., Fored, C. M., MichaelFored, C., Leimanis, A., Otterblad Olausson, P., Bergman, U., Persson, I., Sundström, A., Westerholm, B., & Rosén, M. (2007). The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol. Drug Saf.*, *16*(7), 726–735. https://doi.org/10.1002/pds.1294

Wisniewski, A., Kirchgesner, J., Seksik, P., Landman, C., Bourrier, A., Nion-Larmurier, I., Marteau, P., Cosnes, J., Sokol, H., Beaugerie, L., the Saint-Antoine IBD network, Arrivé, L., Beaugerie, L., Bourrier, A., Camus, M., Chafai, N., Chambenois, E., Chaput, U., Debove, C., Delattre, C., Dray, X., Fléjou, J., Le Gall, G., Hoyeau, N., Kirchgesner, J., Landman, C., Lefèvre, J. H., Marteau, P., Martineau, C., Monnier-Cholley, L., Nion-Larmurier, I., Ozenne, V., Parc, Y., Seksik, P., Sokol, H., Svrcek, M., & Tiret, E. (2020). Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. *United Eur. Gastroenterol. J.*, *8*(3), 303–313. https://doi.org/10.1177/2050640619889763

Ytterberg, S. R., Bhatt, D. L., Mikuls, T. R., Koch, G. G., Fleischmann, R., Rivas, J. L., Germino, R., Menon, S., Sun, Y., Wang, C., Shapiro, A. B., Kanik, K. S., Connell, C. A., & ORAL Surveillance Investigators. (2022). Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N. Engl. J. Med.*, *386*(4), 316–326. https://doi.org/10.1056/NEJMoa2109927

Zabana, Y., Panés, J., Nos, P., Gomollón, F., Esteve, M., García-Sánchez, V., Gisbert, J. P., Barreiro-de-Acosta, M., Domènech, E., & en representación de GETECCU. (2020). The ENEIDA registry (Nationwide study on genetic and environmental determinants of inflammatory bowel disease) by GETECCU: Design, monitoring and functions. *Gastroenterol. Hepatol.*, *43*(9), 551–558. https://doi.org/10.1016/j.gastrohep.2020.05.007

Zhao, M., Gönczi, L., Lakatos, P. L., & Burisch, J. (2021). The Burden of Inflammatory Bowel Disease in Europe in 2020. *J. Crohns Colitis*, *15*(9), 1573–1587. https://doi.org/10.1093/ecco-jcc/jjab029

Zhou, Q., Shen, Z.-F., Wu, B.-S., Xu, C.-B., He, Z.-Q., Chen, T., Shang, H.-T., Xie, C.-F., Huang, S.-Y., Chen, Y.-G., Chen, H.-B., & Han, S.-T. (2019). Risk of Colorectal Cancer in Ulcerative Colitis Patients: A Systematic Review and Meta-Analysis. *Gastroenterol. Res. Pract.*, *2019*, 5363261. https://doi.org/10.1155/2019/5363261

13. APPENDIX

Annex 1 List of Stand-alone Documents

Not applicable.

Annex 2 ENCePP Checklist for Study Protocols

ENCEPP CHECKLIST FOR STUDY PROTOCOLS (REVISION 4)

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

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

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

This Checklist should be included as an Annex by marketing authorization holders when submitting the protocol of a non-interventional PASS to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization 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 GVP.

Study title:

Non-interventional post-authorization prospective cohort study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca®) use in patients with ulcerative colitis: a European multi registry-based study

EU PAS Register® number: to be determined

Study reference number (if applicable):

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

Comments:

none

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	Section 7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Section 7
2.1.2 The objective(s) of the study?	☒	☐	☐	Section 7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Section 8.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	--
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	Section 8.5

Comments:

none

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

[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**
3.3 Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒	☐	☐	Section 8.7.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	--
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:

none

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	Section 8.1 & 8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	Section 5, Section 8.1
4.2.2 Age and sex	☒	☐	☐	Section 8.2.2
4.2.3 Country of origin	☒	☐	☐	Section 8.1 & 8.2
4.2.4 Disease/indication	☒	☐	☐	Section 8.1 & 8.2.2
4.2.5 Duration of follow-up	☒	☐	☐	Section 8.2.4
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 8.2 & 8.4

Comments:

none

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	Section 8.3.3 & Annex 3 - Table 5
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation substudy)	☐	☒	☐	--
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:

none

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 7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Annex 3 - Table 5
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation substudy)	☐	☒	☐	--
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:

none

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	--
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, subgroup 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 & Annex 3 - Table 5
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)	☒	☐	☐	Annex 3 - Table 5
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	--
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, comorbidity, co-medications, lifestyle)	☒	☐	☐	Annex 3 - Table 5

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
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))	☐	☐	☒	--
9.3.3 Covariates and other characteristics?	☐	☒	☐	--
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	Section 8.4

Comments:

none

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?	☐	☒	☐	--
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?	☒	☐	☐	Section 8.7.1
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	--

Comments:

none

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 antifraud 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:

none

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☐	☒	☐	--
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation substudy, 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)	☒	☐	☐	Sections 8.2.4, 8.5, 8.7

Comments:

none

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?	☒	☐	☐	Sections 8.6, 9.4

Comments:

none

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:

none

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 11.1
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Section 11.1

Comments:

none

Name of the main author of the protocol: PPD

Date: 25-Jan-2024

Signature: _____

Annex 3 Additional Information

Variables of Interest

Table 5 Variables of Interest and Their Availability by Registry

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
Variables assessed at baseline (start [index] date of filgotinib)			
Key patient characteristics			
Age: Date/year of birth	yes	yes	yes (Population Register)
Sex	yes	yes	yes (Population Register)
BMI	no (might be in medical report)	yes	yes (SWIBREG, but suboptimal coverage)
Height	yes (not always available; might be in medical report)	yes	yes (SWIBREG, but suboptimal coverage)
Weight	no (might be in medical report)	yes	yes (SWIBREG, but suboptimal coverage)
Dx of UC	yes	yes	yes
Date/year of Dx	yes	yes	yes
Renal impairment (moderate to severe chronic kidney disease [stage 4 or 5])	yes (not always available; might be in medical report [and as described in the medical history of the patient])	yes (creatinine lab values are available)	yes (NPR via ICD10- and NCSP codes) (ICD10-codes: N17 - Acute renal failure N183 - Chronic kidney disease, stage 3 N184 - Chronic kidney disease, stage 4

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	ICC (NL)	SWIBREG (SE)
			N185 - Chronic kidney disease, stage 5 N189 - Chronic kidney disease, unspecified N19 - Unspecified kidney failure Y841- Kidney dialysis Z992 - Dependence on renal dialysis) NCSP-codes: DK001 - Installation of tunnelled hemodialysis catheter DK005 - Tunneled hemodialysis catheter replacement DR014 - Hemodiafiltration DR015 - Hemodialyis, acute DR016 - Hemodialyis, chronic DR020 - Continuous arteriovenous or venovenous hemofiltration DR025 - Preoperative hemodilution DR056 - Heparin-free dialysis DR060 - Home hemodialysis control DR061 - Home hemodialysis start
Severe hepatic impairment (Child Pugh C)	yes (not always available; might be in medical report)	yes	yes (NPR via ICD-codes)

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
UC treatment prior to initiation of filgotinib (specifically other JAKi's; advanced therapies; immunomodulators/immunosuppressants)	yes	yes	yes
JAKi's	yes	yes	yes
Advanced therapies – biologics (including TNFα inhibitors)	yes	yes	yes
Advanced therapies – non-biologics	yes	yes	yes
Immunomodulators /- suppressants (e.g. tacrolimus, azathioprine, mercaptopurine)	yes	yes	yes
Other (aminosalicylates, corticosteroids)	yes (not always available; might be in medical report)	yes	yes
Reasons for switching	yes	yes	yes (SWIBREG, good coverage for targeted therapies)
Intolerance/adverse events	yes	yes	yes
Lack of efficacy	yes	yes	yes
Other	yes	yes	yes
SmPC section 4.1: Indication			
Severity of UC (moderate to severe)	yes (some data in ENEIDA may be available or alternatively through chart abstraction [through proxies such as drug switching, addition of drugs, colectomy etc.])	yes (SCCAI, CRP, fecal calprotectin and if available radiologic and endoscopic information)	yes (Severity of UC based on proxies such as exposure to immunomodulators or different lines of targeted therapies (= moderate to severe UC) or proxies for flares (e.g., steroid prescriptions, steps in the treatment ladder, hospitalizations with UC as main diagnosis, UC-related surgery, extent/location of

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	ICC (NL)	SWIBREG (SE)
			disease in UC, history of prior biologic use, disease duration and UC-related treatment exposure)
Date of severity assessment	yes (if defined by medical therapies)	yes	yes
Date of filgotinib initiation (to ascertain new users) = index date	yes	yes	yes
Age at index date	yes	yes	yes
SmPC section 4.2: Posology (Induction treatment)			
Initial filgotinib dose (induction treatment)	yes (if not available, might be in medical report)	yes	yes
SmPC section 4.3: Contraindications			
Active TB at index date	yes (if not available, might be in medical report)	yes	yes (SmiNet, Population Register)
Dx date TB	yes (if not available, might be in medical report)	yes	yes (SmiNet, Population Register)
Active serious infection (SI) at index date	yes (if not available, might be in medical report)	yes	yes (Population Register, PDR)
Dx date SI	yes (if not available, might be in medical report)	yes	yes (Population Register, PDR)
Current pregnancy at index date	yes (if not available, might be in medical report)	yes	yes (Medical Birth Register)

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
Date of pregnancy	yes	yes	yes (Medical Birth Register)
SmPC section 4.4: Special warnings and precautions for use (Box warning)			
(Age 65+)	yes	yes	yes
Long-time smoking (current or past) for > 10 years	no (if not available, might be in medical report)	no (but can be added)	yes (SWIBREG, but suboptimal coverage [approximately 57%])
Hx of atherosclerotic CVD	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Angina	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Coronary heart disease	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Myocardial infarction	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Congestive heart failure	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Stroke	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Peripheral artery disease	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
Other CV risk factors		yes (as part of medical history/comorbidity)	yes (NPR)
Diabetes mellitus (type 1 or 2)	yes (if not available, might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Hypertension	yes (if not available, might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Obesity/BMI	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Current malignancy	yes (if not available, might be in medical report)	yes (as part of medical history/comorbidity)	yes (Cancer Register)
Hx of malignancy	yes (if not available, might be in medical report)	yes (as part of medical history/comorbidity)	yes (Cancer Register)
SmPC section 4.4: Special warnings and precautions for use: Immunosuppressive medicinal products			
Concomitant use of immunosuppressants/-modulators (e.g. ciclosporin, tacrolimus etc)	yes	yes	yes
Concomitant use of advanced therapies (e.g. biologics [including TNFα- inhibitors], non-biologics [e.g. S1P receptor agonists)	yes	yes	yes
Concomitant use of JAKi's other than filgotinib	yes	yes	yes
SmPC section 4.4: Special warnings and precautions for use: Viral reactivation			
Viral hepatitis	yes	yes	yes (NPR)

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
Dx date of viral hepatitis	Inconsistently (might be in medical report)	yes	yes (NPR)
Herpes zoster (HZ)	yes (if not available, might be in medical report)	yes	yes (NPR)
Dx date of HZ	Inconsistently (might be in medical report)	yes	yes (NPR)
Screening for TB	yes	no	yes (SmiNet)
Date of screening for TB	yes (possibly in ENEIDA or medical history)	no	yes (SmiNet)
Screening for HZ	yes	no	no
Date of screening for HZ	yes (possibly in ENEIDA or medical history)	no	no
Screening for viral hepatitis	yes	yes	no
Date of screening for viral hepatitis	yes	yes	no
SmPC section 4.4: Special warnings and precautions for use: Haematological abnormalities			
Laboratory measurement of ANC	no (might be in medical report)	no (only total leucocyte count, but it can be added)	yes (currently for <20%)
Date of measurement	no (might be in medical report)	yes (leucocyte count at baseline [week 0])	yes (currently for <20%)
Laboratory measurement of ALC	no (might be in medical report)	no (only total leucocyte count, but it can be added)	yes (currently for <20%)
Date of measurement	no (might be in medical report)		yes (currently for <20%)

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
Laboratory measurement of Hb	no (might be in medical report)	yes	yes (currently for <20%)
Date of measurement	no (might be in medical report)	yes	yes (currently for <20%)
SmPC section 4.4: Special warnings and precautions for use: Vaccinations			
Use of live, attenuated vaccines	yes (if not available, might be in medical report)	no (but can be added)	no
Date of vaccine administration	yes		no
HZ vaccination	yes (if not available, might be in medical report)	no (but can be added)	no
Date of vaccine administration	yes		no
SmPC section 4.4: Special warnings and precautions for use: Venous thromboembolism (VTE)			
(Age 65+)	yes	yes	yes
Long-time smoking (current or past) for > 10 years	yes (if not available, might be in medical report)	no (but can be added)	yes (SWIBREG, but suboptimal coverage)
Hx of atherosclerotic CVD	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Angina	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Coronary heart disease	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
Myocardial infarction	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Congestive heart failure	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Stroke	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Peripheral artery disease	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Other CV risk factors		yes (as part of medical history/comorbidity)	yes (NPR)
Diabetes mellitus (type 1 or 2)	yes (if not available, might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Hypertension	yes (if not available, might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Obesity/BMI	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Current malignancy	yes (if not available, might be in medical report)	yes (as part of medical history/comorbidity)	yes (Cancer Register)
Hx of malignancy	yes (if not available, might be in medical report)	yes (as part of medical history/comorbidity)	yes (Cancer Register)

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
Previous VTE	yes (if not available, might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Recent surgery (within 1 month prior to the index date or at any time during follow-up)	no (might be in medical report if related to IBD surgery)	yes (as part of medical history/comorbidity; history and location of IBD surgery is collected, and any IBD-surgery during follow-up)	yes (NPR)
Date of surgery	only IBD-related surgery; others might be in medical report	yes	yes (NPR)
Reduced mobility	no (might be in medical report)	no	yes (immobilization cannot be reliably captured in the Swedish registers; inpatient care due to UC [i.e., UC as main diagnostic listing] which will capture hospitalized patients in NPR; by proxies, e.g. major orthopedic surgery [pelvis/abdomen, hip or knee replacement; knee arthroscopy]; any surgery that requires immobilization post-procedure including fracture surgery and amputation of lower limbs; some types of vascular and orthopedic surgery)
Recent hospitalization (within 1 month prior to the index date or at any time during follow-up)	no (might be in medical report)	yes (hospitalizations are registered during follow-up)	yes (hospitalization record in the inpatient part of the NPR;

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
			hospitalizations with IBD as the main diagnostic listing will be treated as flares)
Date of hospitalization	no (might be in medical report)	yes	yes (NPR)
Hx of blood clotting disorder or blood clots	no (might be in medical report)	yes (as part of medical history/comorbidity)	yes (NPR)
Concomitant use of combined hormonal contraceptives	no (might be in medical report)	no (but can be added)	yes (NPR)
Concomitant use of hormone replacement therapy	no (might be in medical report)	no (but can be added)	yes (NPR)
SmPC section 4.6: Fertility, pregnancy and lactation			
Advice on contraception in women of childbearing potential	no	no	no
Breastfeeding	no (might be in medical report)	no (but can be added)	no
Variables assessed during follow-up			
Filgotininb treatment status			
Discontinuation	yes	yes	yes (SWIBREG, PDR)
Date of discontinuation	yes	yes	yes (SWIBREG, PDR)
SmPC section 4.2: Posology (Maintenance treatment)			
Maintenance filgotinib dose (after a maximum of 22 weeks of induction treatment)	yes (if not available, might be in medical report)	yes	yes (PDR)
SmPC section 4.3: Contraindications			

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
Tuberculosis (TB)	yes (if not available, might be in medical report)	yes	yes (SmiNet)
Dx date TB	yes (if not available, might be in medical report)	yes	yes (SmiNet)
Serious infection (SI)	yes (if not available, might be in medical report; a proxy definition of infection severity can be used to align with the definition of the other registries, based on information available from an eCRF field on the outcome of the infection [such as death, hospital admission])	yes (infections that lead to hospitalization or intravenously administrated antibiotic or antiviral medication)	yes (ICD-10 codes as recorded in the NPR or the 'infectious disease register' [for tuberculosis] including overall codes for e.g. sepsis or septic shock or for specific infectious disease categories being the main or contributory diagnostic listing for a hospitalization)
Dx date SI	yes (if not available, might be in medical report)	yes	yes (NPR)
Pregnancy	yes (if not available, might be in medical report)	yes	yes (Medical Birth Register; could be retrieved following child birth)
Date of pregnancy	yes	yes	yes (Medical Birth Register; could be retrieved following child birth)
SmPC section 4.4: Special warnings and precautions for use: Infections			

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
Acute infection	no (only serious or opportunistic infection can be recorded)	yes	yes (NPR, PDR [prescription of antibiotics])
Dx of acute infection	no	yes	yes (NPR, PDR)
SmPC section 4.4: Special warnings and precautions for use: Viral reactivation	yes (if not available, might be in medical report)		
Viral hepatitis	yes (if not available, might be in medical report)	yes	yes (NPR)
Dx date of viral hepatitis	yes	yes	yes (NPR)
Herpes zoster (HZ)	yes (if not available, might be in medical report)	yes	yes (NPR)
Dx date of HZ	yes	yes	yes (NPR)
SmPC section 4.4: Special warnings and precautions for use: Lipids			
Laboratory measurement of total cholesterol	no (might be in medical report)	no (but will be added)	no
Date of measurement	no (might be in medical report)	(at baseline, week 0), and at follow-up week 12,24, 52 and the year 1, 2, 3 …)	
Laboratory measurement of HDL	no (might be in medical report)	no (but will be added)	no
Date of measurement	no (might be in medical report)	(at baseline, week 0), and at follow-up week 12,24, 52 and the year 1, 2, 3 …)	no

Variable	Availability in individual registries yes/no (additional comments)		
	ENEIDA (ES)	**ICC (NL)**	**SWIBREG (SE)**
Laboratory measurement of LDL	no (might be in medical report)	no (but will be added)	no
Date of measurement	no (might be in medical report)	(at baseline, week 0), and at follow-up week 12,24, 52 and the year 1, 2, 3 …)	no
Laboratory measurement of triglycerides	no (might be in medical report)	no (but will be added)	no
Date of measurement	no (might be in medical report)	(at baseline, week 0), and at follow-up week 12,24, 52 and the year 1, 2, 3 …)	no
Laboratory measurement of HDL:LDL	no (might be in medical report)	no (but will be added)	no
Date of measurement	no (might be in medical report)	(at baseline, week 0), and at follow-up week 12,24, 52 and the year 1, 2, 3 …)	no
SmPC section 4.4: Special warnings and precautions for use: Haematological abnormalities			
Same as for baseline assessment	no (might be in medical report)	yes	yes (currently for <20%)
SmPC section 4.4: Special warnings and precautions for use: VTE			
VTE event during FU (including PE and deep vein thrombosis)	yes (if not available, might be in medical report)	yes	yes (NPR)
Dx date of VTE	yes	yes	yes (NPR)

ALC = absolute lymphocyte count; ANC = absolute neutrophil count; BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; Dx = diagnosis; Hb = hemoglobin; HDL = high-density lipoprotein; Hx = history; HZ = herpes zoster; IBD = inflammatory bowel disease; ICD = International Classification of Diseases; JAKi = Janus kinase inhibitor; LDL = low density lipoprotein; MACE = major cardiovascular event; NCSP = NOMESCO Classification of Surgical Procedures; NPR = National Patient Register; PE = pulmonary embolism; PDR = Prescribed Drug Register S1P = sphingosine-1-phosphate; SCCAI = Simple Clinical Colitis Activity Index; SI = serious infection; SI = serious infection; SmiNet = Swedish Contagious Disease Register; SmPC = Summary of Product Characteristics; TB = tuberculosis; TNF = tumour necrosis factor; UC = ulcerative colitis; VTE = venous thromboembolism

SIGNATURE PAGE – INVESTIGATOR

Study Title: Non-interventional post-authorization cohort study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca®) use in patients with ulcerative colitis within European registries

Non-interventional Study Protocol Version: 3.0 **Date**: 25-Jan-2024

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 Practices and Heads of Medicines Agencies Good Pharmacovigilance Practices.

Investigator Name	Signature	Date

SIGNATURE PAGE – SPONSOR

Study Title: Non-interventional post-authorization cohort study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca®) use in patients with ulcerative colitis within European registries

Non-interventional Study Protocol Version: 3.0 **Date**: 25-Jan-2024

This non-interventional 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.

Electronic signatures of the sponsor are provided at the end of the document

Non-interventional Study Lead	Signature	Date
Qualified Person for Pharmacovigilance	Signature	Date

Signature Page for glpg0634-cl-417-protocol 26717

Approval	PPD ogy Leader Medical Safety 25-Jan-2024 09:38:51 GMT+0000

Approval	PPD Medical Safety 25-Jan-2024 12:55:20 GMT+0000

Signature Page for glpg0634-cl-417-protocol43952_85487_129556