EU RISK MANAGEMENT PLAN FOR JYSELECA (FILGOTINIB)

Status:	Final		
RMP Version Number:	7.0	Date of Final Sign-off:	28-Feb-2024
Marketing Authorisation Holder:	Galapagos NV Generaal De Wittelaan L11, A3, 2800 Mechelen Belgium		
Signature:	Koen van der Heijden Qualified Person for Pharmacovigilance		

EU RISK MANAGEMENT PLAN FOR JYSELECA® (FILGOTINIB)

Risk Management Plan (RMP) Version to be Assessed as Part of This Application

RMP Version Number	Data Lock Point for This RMP	Date of Final Sign-off
7.0	31 October 2023	28 February 2024

Rationale for Submitting an Updated RMP

To support the Type II variation application (procedure number EMEA/H/005113/II/0031/G) upon completion of the GLPG0634-CL-205 (DARWIN 3) clinical study and clinical study report, combined with the addition of fractures as an important potential risk (EMEA/H/C/PSUSA/00010879/202209).

Summary of Significant Changes in This RMP

Part	Module/Annex	Significant changes to RMP
Part I	Part I: Product Overview	Updated pharmacotherapeutic group (ATC code). Dosage in EEA for rheumatoid arthritis (RA) and UC was moved from 'proposed' to 'current'.
Part II Safety Specification	Part II: Module SI: Epidemiology of the indication and target populations(s)	Shortened the epidemiology section and partially re-arranged the content. Added new information on fractures.
	Part II: Module SII: Non-clinical part of the safety specification	None.
	Part II: Module SIII: Clinical trial exposure	Updated clinical trial exposure data for ongoing blinded studies and completed or open-label studies cumulative for all indications and separately for subjects in RA and UC studies.
	Part II: Module SIV: Populations not studied in clinical trials	None.
	Part II: Module SV: Post-authorisation experience	Updated post-authorisation exposure to Jyseleca for all indications.
	Part II: Module SVI: Additional EU requirements for the safety specification	None.
	Part II: Module SVII: Identified and potential risks	Added fractures as an important potential risk.
	Part II: Module SVIII: Summary of the safety concerns	Added fractures as an important potential risk under summary of safety concerns.

Part	Module/Annex	Significant changes to RMP
Part III Pharmacovigilance Plan		Updated rationale, milestones, and due dates for ongoing and planned additional pharmacovigilance activities.
Part IV Plan for post-authorisation efficacy studies		None.
Part V Risk Minimisation Measures		Updated routine risk minimisation measures for fractures. Clarified measurement of effectiveness of patient alert cards for specific PASS described in the RMP. Updated summary of pharmacovigilance activities and risk minimisation activities by safety concern.
Part VI Summary of RMP		Addition of fractures as an important potential risk.
Part VII Annexes		Updates to: Annex 2 Annex 3 Annex 8

Other RMP Versions Under Evaluation

None.

Details of the Currently Approved RMP

RMP Version Number	Approved With Procedure	Date of Approval (Opinion Date)
6.0	EMEA/H-A20/1517/C/005113/0014	10 March 2023

Qualified Person for Pharmacovigilance (QPPV) Name: Koen van der Heijden

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. An electronic signature is provided at the end of the document.

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LIST OF ABBREVIATIONS

Ab	antibody
ACPA	anti-citrullinated protein antibody
ACR	American College of Rheumatology
ADA	adalimumab
ADR	adverse drug reaction
AE	adverse event
AS	ankylosing spondylitis
ASA	aminosalicylate
ASDAS	ankylosing spondylitis disease activity score
AUC	area under the plasma/serum concentration versus time curve
BCRP	breast cancer resistance protein
bDMARD	biologic DMARD
BID	twice daily
BMI	body mass index
CD	Crohn's disease
CDAI	Clinical Disease Activity Index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIA	collagen-induced arthritis
CKD	chronic kidney disease
CLE	cutaneous lupus erythematosus
CMV	cytomegalovirus
CNS	central nervous system
CNTF	ciliary neurotrophic factor
COPD	chronic obstructive pulmonary disease
CRC	colorectal cancer
CrCl	creatinine clearance

CRP	C-reactive protein
csDMARD	conventional synthetic DMARD
CTCAE	Common Terminology Criteria for Adverse Events
CTD	connective tissue disease
CV	cardiovascular
CYP	cytochrome P450 enzyme
DAS28	Disease Activity Score 28 joints
DAS28-CRP	Disease Activity Score for 28 joint count using C-reactive protein
DDI	drug-drug interactions
DMARDs	disease-modifying antirheumatic drugs
DNA	deoxyribonucleic acid
DUS	drug utilisation study
DVT	deep vein thrombosis
EC	European Commission
ECG	electrocardiogram
EFD	embryo-fetal development
EMA	European Medicines Agency
EPO	erythropoietin
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
EU-RMP	EU Risk Management Plan
EAER	exposure-adjusted event rate
EAIR	exposure-adjusted incidence rate
FAS	Full Analysis Set
FSH	follicle stimulating hormone
Galapagos	Galapagos NV
GC	glucocorticoid

GEE	generalized estimating equations
GFR	glomerular filtration rate
GH	growth hormone
GI	gastrointestinal
Gilead	Gilead Sciences
GLP	Good Laboratory Practice
GM-CSF	granulocyte monocyte colony-stimulating factor
GS-6034	filgotinib (free base)
GS-829845	major human metabolite of filgotinib
HAQ-DI	Health Assessment Questionnaire-Disability Index
HAS	human serum albumin
HBV	hepatitis B virus
HCP	healthcare professional
HCV	hepatitis C virus
hERG	human Ether-à-go-go-Related Gene
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HZ	herpes zoster
IB	investigator's brochure
IBD	inflammatory bowel disease
IC_{50}	half-maximal inhibitory concentration
IFN	interferon
IL	interleukin
IL-6	interleukin-6
IRR	Incidence rate ratio
IPAA	ileal pouch-anal anastomosis
ISE	integrated summary of efficacy
ISS	integrated summary of safety

JAK	Janus kinase
JAKi	JAK inhibitor
JIA	juvenile idiopathic arthritis
LH	luteinizing hormone
LIF	leukemia inhibitory factor
LMN	lupus membranous nephropathy
LTE	long-term extension
MAA	marketing authorisation application
MACE	major cardiovascular adverse events
MATE	multidrug and toxin extrusion
MCS	Mayo clinic score
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
MST	MedDRA search term
MTX	methotrexate
NCA	non-compartmental analysis
NMSC	non-melanoma skin cancer
NOAEL	no observed adverse effect level
NRI	nonresponder imputation
NSAID	nonsteroidal anti-inflammatory drug
OAT	organic anion transporter
OI	opportunistic infection
OR	odds ratio
PAC	patient alert card
PBRER	periodic benefit-risk evaluation report
PCP	pneumocystis pneumonia
PE	pulmonary embolism
PGA	physician global assessment

P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
popPK	population pharmacokinetic
PL	package leaflet
PRL	prolactin
PRO	patient-reported outcome
PsA	psoriatic arthritis
PSUR	periodic safety update report
PT	Preferred term
PUFA	polyunsaturated fatty acid
PV	pharmacovigilance
PTM	placebo-to-match
PYE	patient-years of exposure
q.d.	once daily
RA	rheumatoid arthritis
RF	rheumatoid factor
RMM	risk minimisation measure
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SDAI	Simplified Disease Activity Index
SJC	swollen joint count
SJC66	swollen joint count based on 66 joints
SjS	Sjögren’s syndrome
SLE	systemic lupus erythematosus
SmPC	summary of product characteristics
SOC	System Organ Class

STAT	signal transducer and activator of transcription
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TJC68	tender joint count based on 68 joints
TNF	tumor necrosis factor
TPO	thrombopoietin
TYK	tyrosine kinase
UC	ulcerative colitis
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
US	United States
VZV	varicella zoster virus
VTE	venous thromboembolism

PART I: PRODUCT OVERVIEW

Table 1: Product Overview

Active substance(s) (INN or common name)	Filgotinib
Pharmacotherapeutic group(s) (ATC Code)	L04AF04 (Immunosuppressants, Janus-associated kinase inhibitors)
Marketing Authorisation Holder	Galapagos NV
Medicinal products to which this RMP refers	Filgotinib
Invented name(s) in the European Economic Area (EEA)	Jyseleca
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Janus kinase inhibitor (JAKi)
	Summary of mode of action: Filgotinib is an adenosine triphosphate competitive and reversible inhibitor of Janus kinase (JAK) family. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor receptor interactions on the cellular membrane to influence cellular processes of haematopoiesis, cytokine signalling and immune cell function. Within the signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity including gene expression. Filgotinib modulates the signalling pathway by preventing the phosphorylation and activation of STATs. In biochemical assays, filgotinib preferentially inhibited the activity of JAK1. In human cellular assays, filgotinib preferentially inhibited JAK1/JAK3, with functional selectivity over cytokine receptors that signal via pairs of JAK2 or JAK2/TYK2.
	Important information about its composition: None
Hyperlink to the Product Information	Jyseleca Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: Rheumatoid arthritis Jyseleca is indicated for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Jyseleca may be used as monotherapy or in combination with methotrexate (MTX). Ulcerative colitis Jyseleca is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.

	Proposed: Not applicable.
Dosage in the EEA	Current: Rheumatoid arthritis The recommended dose of filgotinib for adult patients is 200 mg once daily. In adults at increased risk of venous thromboembolism (VTE) , major cardiovascular adverse events (MACE), and malignancy (see Section 4.4 of the SmPC), the recommended dose is 100 mg once daily and may be escalated to 200 mg once daily in case of insufficient disease control. For long-term treatment, the lowest effective dose should be used. In patients with RA aged 65 years of age and older, the recommended dose is 100 mg once daily and may be escalated to 200 mg once daily in case of insufficient disease control (see Section 4.4 of the SmPC). For long-term treatment, the lowest effective dose should be used. Ulcerative colitis Induction treatment The recommended dose for induction treatment is 200 mg once daily. For patients with UC who do not show an adequate therapeutic benefit during the initial 10 weeks of treatment, 12 additional weeks of induction treatment with filgotinib 200 mg once daily may provide additional relief of symptoms (see Section 5.1 of the SmPC). Patients who have not shown any therapeutic benefit after 22 weeks of treatment should discontinue filgotinib. Maintenance treatment The recommended dose for maintenance treatment is 200 mg once daily. In adults at higher risk of VTE, MACE, and malignancy (see Section 4.4 of the SmPC), the recommended dose for maintenance treatment is 100 mg once daily. 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. In patients with UC aged 65 years of age and older, the recommended dose is 200 mg once daily for induction treatment and 100 mg once daily for maintenance treatment (see Section 4.4 of the SmPC). 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. Filgotinib is not recommended in patients 75 years and older as there is no data in this population. A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (creatinine clearance [CrCl] 15 to <60 mL/min).
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Each film-coated tablet contains filgotinib maleate equivalent to 100 mg or 200 mg of filgotinib.
	Proposed: Not applicable

Is/will the product be subject to additional monitoring in the EU?	Yes

ATC = anatomical therapeutic chemical; EEA = European Economic Area; EU = European Union; INN = international nonproprietary name; RMP = Risk Management Plan

PART II: SAFETY SPECIFICATION

PART II: MODULE SI – EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Rheumatoid Arthritis

RA is a chronic inflammatory disease that primarily involves the synovial joints and leads to cartilage and bone damage. Other extra-articular manifestations can occur, such as rheumatoid nodules, pulmonary disease, and vasculitis. The presence of autoantibodies (seropositivity) against citrullinated peptides (ACPAs) and/or rheumatoid factor (RF) is associated with more severe symptoms and joint damage, and increased mortality (Smolen et al. 2016). Immune activation leads to synovial membrane inflammation and joint swelling. Articular destruction is caused by activated synovial fibroblasts, enhanced chondrocyte catabolism and synovial osteoclastogenesis.

The affected patient may present with symptoms such as joint pain, swelling, fatigue and morning stiffness. Laboratory tests may reveal elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). Other causes of arthritis need to be excluded (e.g. osteoarthritis, psoriatic arthritis, infectious arthritis and other autoimmune conditions).

RA affects adults of any age and prevalence increases with age; the peak age of onset is between 40 to 60 years and prevalence is highest at age 70 years and over. Around three-quarters of people with RA are of working age when they are first diagnosed (Arthritis 2019).

According to the Global Burden of Disease study (data from 195 countries), the incidence (in thousands) of RA worldwide in 2016 was 1174 with an incidence rate of 0.02% (GBD et al. 2017). RA incidence varied greatly among different European countries (Table 2). A systematic review of incidence studies showed that South European countries had a lower median annual incidence rate of RA (0.0165%) than North American (0.038%) and North European countries (0.029%) (Alamanos et al. 2006).

Table 2: Incidence Rates of Rheumatoid Arthritis in European Countries

Country	Age Group (years)	Incidence Rate (%)	95% Confidence Interval (%)	Men (%)	Women (%)
Finland (Kononoff et al. 2017)	16+	0.0416	0.0333-0.0514	0.0425	0.0408
Germany (Steffen et al. 2017)	18+	0.08	unspecified	0.054	0.104
Italy (DeSocio et al. 2018)	18+	0.0214	unspecified	0.0076	0.0336
Spain (Carbonell et al. 2008)	17+	0.0083	0.0075-0.0092	0.0052	0.0113
UK (Abhishek et al. 2017)	18+	0.0381	0.0361-0.0402	0.0251	0.0509

Results from the Global Burden of Disease 2016 study (data from 195 countries) found that the prevalence (in thousands) of RA worldwide in 2016 was 21,337 with a prevalence rate of 0.29% (GBD et al. 2017).

The prevalence of RA varies among European countries (Table 3) and other areas of the world.

Table 3: Prevalence of Rheumatoid Arthritis in European Countries

Country	Age Group (years)	Prevalence (%)	95% Confidence Interval (%)	Men (%)	Women (%)
England (Arthritis 2019)	17+	0.84	unspecified	unspecified	unspecified
Denmark (Kiadaliri et al. 2018)	unspecified	0.26-0.63	0.26 (0.24-0.29) 0.63 (0.57-0.70)	0.26	0.63
Finland (Kiadaliri et al. 2018)	unspecified	0.32-0.77	0.32 (0.29-0.36) 0.77 (0.70-0.84)	0.32	0.77
France (Roux et al. 2007)	All ages	0.31	0.18-0.48	0.09	0.51
Germany (Steffen et al. 2017)	18+	1.23	unspecified	0.70	1.70
Greece (Anagnostopoulos et al. 2010)	20+	0.57	0.32-0.87	Unspecified, but women: men ratio is 2.3:1.	
Italy (Salaffi et al. 2005; Atella et al. 2019)	35+	0.8	unspecified		
Norway (Kiadaliri et al. 2018)	unspecified	0.25-0.57	0.25 (0.23-0.28) 0.57 (0.51-0.63)	0.25	0.57
Poland (Iltchev et al. 2016; Batko et al. 2019)	15+	0.9	0.6-1.2	0.74	1.06
Scotland (Arthritis 2019)	19+	0.78	unspecified		
Spain (Carmona et al. 2002)	20+	0.5	0.25-0.85	0.2	0.8
Sweden (Kiadaliri et al. 2018)	unspecified	0.24-0.53	0.24 (0.21-0.26) 0.53 (0.48-0.60)	0.24	0.53
UK (Abhishek et al. 2017)	18+	0.67	0.66-0.67	0.40	0.93

The variability in the reported incidence and prevalence estimates of RA among studies might be explained by regional differences, environmental and epigenetic conditions. Some methodological aspects also might have a strong influence on the estimates, such as reporting methods, diagnostic criteria, etc. (Scublinsky and Gonzalez 2016).

RA is 2- to 3-times more common among women than men (Arthritis 2019). Table 2 and Table 3 demonstrate that both the incidence and prevalence estimates of RA are higher among women than men.

RA affects adults of any age and prevalence increases with age; the peak age of onset is between 40 to 60 years and prevalence is highest at age 70 years and over. Around three-quarters of people with RA are of working age when they are first diagnosed (Arthritis 2019).

Geographical differences have been reported in European populations – for example, lower incidence and prevalence were reported in Southern Europe than in Northern Europe (Alamanos et al. 2006). Data from GBD 2017 showed that lower incidence and prevalence estimates were also found in Eastern Europe than in Western Europe.

Genetic factors account for the major risk for developing RA, and over 30 genetic factors are found to be associated with RA. A meta-analysis showed that the possession of the G allele of rs41423247 (Bcl-I) may be significantly associated with a lower risk of RA (odds ratio [OR] 0.79, 95% CI: 0.64 – 0.99) among Caucasians (Herrera et al. 2018). Smoking is the dominant environmental risk factor for anti-citrullinated protein antibody (ACPA)-positive (seropositive) disease and doubles the risk of developing RA (Scott et al. 2010). Other risk factors that have been proposed include alcohol intake, coffee intake, oral contraceptive use and low socioeconomic status. Living near air pollution emitters was found to be associated with higher risks of developing RA and of producing RA-specific autoantibodies (Sigaux et al. 2019). Data also suggests that oral, bronchial, and/or intestinal microbiome plays a role in autoimmune and rheumatic diseases. Diabetes and elevated fasting glucose at RA diagnosis were also shown to be associated with poor clinical and radiographic outcomes of early RA (Daïen et al. 2018). Periodontal disease and obesity have been reported to be associated with an increased risk of developing RA (Smolen et al. 2018).

A matched case-control study from the US identified certain comorbidities as risk factors for RA and their accrual after RA diagnosis. The results showed that inflammatory bowel disease (IBD) and type 1 diabetes might predispose patients to RA development, whereas cardiovascular disease, VTE, and obstructive sleep apnea could result from RA (Kronzer et al. 2019).

Treatment is generally directed at suppressing inflammation, which is the driver for clinical symptoms, joint damage, disability and comorbidities. The American College of Rheumatology Guideline and European League Against Rheumatism (EULAR) criteria for the treatment of RA strongly recommends a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity (Aletaha et al. 2010; Singh et al. 2016; Smolen et al. 2020). The ideal target should be low disease activity or remission, depending on the individual's disease duration.

DMARDs target inflammation and reduce progression of structural damage. DMARDs are classified as synthetic (conventional or targeted) and biologic (including biosimilar agents). Examples of available conventional synthetic (cs) DMARDs include MTX, sulfasalazine, leflunomide, and hydroxychloroquine. Examples of targeted synthetic (ts) DMARDs include JAK inhibitors (e.g. tofacitinib, baricitinib, upadacitinib). Examples of biological (b) DMARDs include tumor necrosis factor (TNF) inhibitors (e.g. adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol), anti-CD20 antibodies (e.g. rituximab), anti-T-cell co-stimulators (e.g. abatacept), and anti-interleukin 6 pathway antibodies (e.g. tocilizumab, sarilumab).

Other drugs commonly used include nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs). NSAIDs reduce pain and stiffness and improve physical functioning, but do not reduce joint damage. Glucocorticoids also offer symptomatic benefits and disease-modifying effects but are associated with serious long-term side effects.

The 2020 EULAR recommendations on RA management points out that, MTX alone or in combination with GCs or other csDMARDs remain the recommended first-line therapy. In case of insufficient response to the first-line therapy within 3 to 6 months, risk stratification of an individual patient for bDMARD/tsDMARD (JAKi) initiation based on presence of good or bad prognostic factors is recommended. With poor prognostic factors (presence of autoantibodies, high disease activity, early erosions or failure of 2 csDMARDs), any bDMARD or JAK inhibitor should be added to the csDMARD. If this fails, any other bDMARD (from another or the same class) or tsDMARD is recommended. On sustained remission, DMARDs may be tapered but should not be stopped (Smolen et al. 2020, 2023).

Patients with RA are commonly treated with multiple medications, which can include GCs, NSAIDs, MTX, and other DMARDs. Patients are also monitored and treated for comorbidities, which influences treatment options for RA. Common examples include chronic infections such as hepatitis B, hepatitis C and tuberculosis, cardiovascular disease such as congestive heart failure, and cancers.

Analgesics, such as NSAIDs, may provide temporary pain relief, however they are not recommended as sole or primary therapy in patients with active inflammatory disease.

People with RA are adversely affected by musculoskeletal deficits with decline in physical function and quality of life. Social economic consequences include direct medical costs, reduced work capacity and decreased societal participation.

RA develops in a series of phases. It starts with the presence of genetic and/or environmental risk factors that trigger RA without detectable systemic autoimmunity in the blood. After this phase, autoimmunity may be detectable through serologic or other testing (e.g. autoantibodies, autoreactive cells) in peripheral blood. This is followed by a propagation phase that is characterised by an expansion of autoimmunity, inflammation and symptoms. Eventually, clinically detectable inflammatory arthritis develops and can be classified as RA (Deane and Holers 2019). The clinical course of the disease is variable. About 15 to 20% of patients will have intermittent disease with periods of exacerbation and a relatively good prognosis. Most patients will, however, have progressive disease, that either takes a slow or rapid course. In the first 2 years of the disease, approximately 70% of patients will have evidence of joint erosion detectable by X-ray in the hands and feet (Heijde 1995). After 20 years of living with the disease, over 60% of patients with RA will be in functional class III (significantly impaired, self-caring, using aids, requiring joint replacements) or class IV (loss of independence requiring daily care). Increased rates of fracture have been described in RA with incidence rates ranging from 0.51 to 3.30 per 100 patient-years (Kim et al. 2012; Xue et al. 2017; Jin et al. 2018). A recent meta-analysis conducted by Xue et al., 2017 found patients with RA have a 2.25 times greater risk of any fracture compared to the general population (95% CI: 1.76–2.87). Risk of vertebral (relative risk [RR]: 2.93, 95% CI: 2.25–3.83) and hip (RR: 2.41, 95% CI: 1.83–3.17) fractures was also found to be higher in RA populations compared to non–diseased populations (Xue et al. 2017).

Patients with RA have an increased incidence of infection (e.g. pulmonary, skin and joint infection) (Ramiro et al. 2014; Chen et al. 2017), cardiovascular disease (Lindhardsen et al. 2012; Chung et al. 2014), lymphoproliferative disorders (e.g. lymphomas) and other malignancies (e.g. non-melanoma skin cancer, lung cancer). In a matched-cohort study in Sweden, which followed 12,656 incident cases of RA and 776,578 person-years of follow-up, patients with RA had a hazard ratio for lymphoma of 1.6 (95% CI: 1.2-2.1) compared to the general population (Hellgren et al. 2017). A systematic review and meta-analysis showed that, patients with RA appeared to be at a higher risk of lymphoma, melanoma and lung cancer and potentially decreased risk for colorectal and breast cancer compared with the general population; whereas cervical cancer and prostate cancer appeared to show no consistent trend in risk among RA patients compared with the general population (Simon et al. 2015). Another systematic review and meta-analysis showed that the patients with RA had a higher risk of overall fracture (RR 1.52, 95% CI: 1.07-2.14) and fragility fractures (RR 1.61, 95% CI: 1.44-1.79) (Jin et al. 2018).

Due to improvements in early diagnosis and treatment of RA, global mortality has decreased among RA patients over the past decades but it remains higher than in the general population (Dadoun et al. 2013). The risk of death is increased 47% among people with RA when compared with the general population, matched for age and sex (Arthritis 2019). RA contributes to a reduction in life expectancy of 8 to 15 years, which is mainly attributable to the increased prevalence of coronary artery disease and heart failure in RA patients (Schau et al. 2015). A cohort study also revealed that mortality rates for all-cause and specific causes were increased in RA patients compared with the general population (232 [95% CI: 228-236] versus 184 [95% CI: 182-186] per 10,000 person-years) (Widdifield et al. 2018). In another study, age-specific mortality ratios demonstrated a high excess mortality among RA patients younger than 45 years of age for respiratory disease and circulatory disease (Widdifield et al. 2018).

Patients with RA are reported to have a higher risk of developing comorbidities and premature mortality compared with non-RA controls. Understanding the burden of comorbidities in RA will provide important insights into disease management strategies (Norton et al. 2013; Dougados et al. 2014; Agca et al. 2017; An et al. 2019). The estimated prevalence of comorbidities varies based on the study population, settings, and definition of comorbidities in different studies. The most important comorbidities are listed below.

- Cardiovascular and non-cardiac vascular disease (e.g. myocardial infarction, heart failure, stroke, hyperlipidaemia, hypertension, thromboembolism)
- Chronic pain
- Respiratory disorders (e.g. asthma, chronic obstructive pulmonary disease [COPD])
- Psychological disorders (e.g. anxiety, depression, dementia)
- Diabetes
- Chronic kidney disease (CKD)
- Malignancies (e.g. non-melanoma skin cancer, non-Hodgkin’s lymphoma, leukemia, lung cancer)
- Musculoskeletal disorders (e.g. osteoporosis)
- Infection (herpes zoster, hepatitis, tuberculosis, pneumonia)

- Gastrointestinal ulcers
- Alcohol/drug abuse
- Anemia of chronic disease.

SI.2 Ulcerative Colitis

UC is an immune-mediated, chronic idiopathic 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.

UC most commonly affects adults aged 30 to 40 years, without specific sex predominance components (Ungaro et al. 2017; Feuerstein et al. 2019; Gajendran et al. 2019). It is more common in industrialized countries, but there is a worldwide increase in prevalence and incidence, especially in Asia (Kobayashi et al. 2020; Zhao et al. 2021).

The overall annual cumulative UC incidence is reported to be in the range of 1.2 to approximately 44 per 100000 persons (Burisch et al. 2013, 2014; Ungaro et al. 2017; Zhao et al. 2021), with the highest incidence reported in Northern Europe and the United Kingdom (UK) (Burisch et al. 2013; Ungaro et al. 2017). In Europe, the overall age- and sex-adjusted annual incidence rate (IR) 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). Within a defined geographical area, incidence rates and their patterns vary. Incidence is higher in urban than in rural populations, and the increase in incidence in urban communities preceded that in rural ones by 1 decade (Ananthakrishnan 2015).

In Europe, the prevalence of UC ranges from 2.4 (Romania) to >600 (UK) per 100000 (Ananthakrishnan 2015; Ng et al. 2017; Brunet et al. 2018; Macaluso et al. 2019; King et al. 2020).

As the incidence of UC is increasing or stable in virtually every region of the world, the prevalence of UC is increasing further due to the early age of onset and low mortality of UC patients (Burisch et al. 2013). For example, the age- and sex-adjusted prevalence for UC in Catalonia, Spain was 353.9 per 100,000 in 2016 compared with 268.4 per 100,000 in 2011 (Brunet et al. 2018).

The prevalence of UC varies among other geographical regions, and ranges from 37.5 to 248.6 per 100,000 persons in North America, 12.5 in Puerto Rico and 14.8 in Brazil, and from 4.9 to 168.3 per 100,000 persons in Asia and the Middle East (Molodecky et al. 2012; Silva et al. 2014). High prevalence rates were reported for Nova Scotia, Canada in 2008 (870 per 100,000 persons) (Kaplan et al. 2019), the US (286 per 100,000 persons) (Shivashankar et al. 2017), and Australia (131.4 per 100,000 persons) (Bhatia et al. 2019).

Most studies have shown an equal gender distribution of UC. According to a recent pooled analysis of population based studies from western countries, the incidence rates of UC were similar for females and males until middle age (40-44 years of age) with the exception of early

childhood (5-9 years of age), where females had a 22% higher risk of being diagnosed with UC versus males (incidence rate ratio [IRR], 1.22; 95% CI, 1.05-1.41) (Shah et al. 2018).

The age of onset of most UC cases is 15 to 40 years of age, with the peak between 30 and 40 years of age (Ungaro et al. 2017). Elderly-onset (>60 years of age) incidence rates ranged from 7 to 29% of all UC patients (Kedia et al. 2018). Of patients with elderly-onset UC, 65% were diagnosed during the sixth decade, 25% during the seventh decade, and 10% during the eighth decade (Kedia et al. 2018). Overall, the incidence rates of UC in the elderly in Europe, the US, and Canada were higher than rates of Crohn's disease (CD), with the incidence of UC rising at a faster rate than CD incidence (Stepaniuk et al. 2015).

Multiple intrinsic and extrinsic risk factors have been implicated in the development of UC.

A positive family history is an independent risk factor, as approximately 8 to 14% of UC patients may have a family history of IBD, with a 4-fold increased risk of developing UC in first-degree family members (Ungaro et al. 2017).

Several medications have been associated with an increased risk of UC: oral contraceptives, hormone replacement therapy, and nonsteroidal anti-inflammatory agents. Users of oral contraceptives were reported to have an increased risk of UC (OR, 1.25; 95% CI, 1.04-1.51, p=0.02 in ever users, and 1.49; 95% CI, 1.12-1.96, p=0.005 in current users) (Wang et al. 2019). An umbrella review of meta-analyses also reported a significant association between oral contraceptive use and UC (OR, 1.28; 95% CI, 1.08-1.52), with some evidence to suggest greater risk with longer exposure (Piovani et al. 2019). Postmenopausal hormone therapy was also shown to increase the risk of UC among participants in the Nurses' Health Study, with a multivariate-adjusted hazard ratio for UC of 1.71 (95% CI, 1.07-2.74) for women who currently used hormones and 1.65 (95% CI, 1.03-2.66) for past users. The risk of UC appeared to increase with longer duration of hormone use (P_{trend}=0.04) and decreased with time since discontinuation (Khalili et al. 2012). Also, among women enrolled in the Nurses' Health Study, those who used nonsteroidal anti-inflammatory drugs ≥15 days per month were at increased risk for UC (multivariate hazard ratio, 1.87; 95% CI, 1.16-2.99) (Ananthakrishnan et al. 2012). The risk of UC has been shown to be higher in people residing in urban areas (IRR 1.17; 95% CI, 1.03-1.32) (Piovani et al. 2019).

In addition, breast feeding, vegetarian diet, and increase in intake of long chain n-3 polyunsaturated fatty acids (PUFAs) were associated with decreased risk of UC, whereas dietary n-6 PUFA intake and animal protein were associated with increased risk of UC (Klement et al. 2004; Jantchou et al. 2010; Silva et al. 2010; Ananthakrishnan et al. 2014; Amarapurkar et al. 2018; Piovani et al. 2019). Being ever breastfed has been shown to be protective for developing UC (OR, 0.78; 95% CI, 0.67-0.91), with longer exposures associated with greater protective effects and a stronger effect in Asian versus white populations (Piovani et al. 2019). Consumption of tea has been shown to be protective for UC (risk ratio, 0.69; 95% CI, 0.58-0.83) while soft drinks increased the risk (risk ratio, 1.69; 95% CI, 1.24-2.30) (Jantchou et al. 2010). A meta-analysis of cohort and case-control studies examined the association of total dietary intake of carbohydrates and reported no increased risk for UC (pooled OR, 1.010; 95% CI, 0.630-1.618) (Jin et al. 2019). For other dietary factors, such as intake of vegetable protein, fat, sugar, and

starch, insufficient evidence was found for an association with the risk of UC (Jantchou et al. 2010; Chan et al. 2014).

The gut microbiome may play a role in UC pathogenesis as multiple studies have documented differences in the composition of the gut flora (dysbiosis) between patients with IBD and healthy individuals, particularly with respect to microbial diversity and the relative abundance of specific bacterial taxa. While dysbiosis is currently recognised as a potential factor contributing to the disease state in patients with UC, the available studies on gut microbiota in IBD patients are largely retrospective, examining the microbiome after the disease onset. Therefore, the question of whether dysbiosis is truly causative or possibly secondary to the inflammatory state requires further research (Ni et al. 2017; Khan et al. 2019).

The treatment paradigm for UC has historically comprised an initial treatment for acute disease, with the goal of inducing a state of clinical remission, followed by a therapeutic intervention to maintain remission. Generally, patients presenting with mild to moderate disease activity are initially administered an anti-inflammatory agent such as a 5-aminosalicylate (5-ASA) derivative, with or without concurrent corticosteroids. Patients who fail to respond to initial therapy or who present with moderate to severe disease activity require treatment with more effective agents. In recent years, a significant shift has occurred in the treatment of UC, as demonstrated by the substitution of general immunosuppressants (corticosteroids and immunomodulators) with targeted biologics. For nearly 2 decades, biological therapies were dominated by anti-TNF-α agents but more recently have included vedolizumab, an injectable integrin α4β7 monoclonal antibody (Feagan et al. 2013), and ustekinumab, an IL-12 and IL-23 inhibitor (Sands et al. 2019). Tofacitinib, a JAK 1/3 inhibitor, was approved in 2018 for the treatment of moderately to severely active UC.

Although biological therapies have led to substantial improvements in the care of patients with UC and have become an integral part of standard therapy, not all treated patients benefit from these therapies (Duijvestein et al. 2018). Depending on the duration of therapy and the clinical endpoints chosen, approximately one-third of patients do not respond after initiation of biological therapy (primary nonresponse). Among patients who initially respond to treatment with biological therapies, 30 to 50% eventually stop responding (secondary nonresponse), resulting in exposure to potential side effects and toxicities without durable clinical benefit. These findings highlight the unmet medical need in these patients.

In addition to the UC treatment medications, other medications used can include antibiotics, antidiarrheal medications, analgesics, and iron supplements. Medications for the treatment of other age-related diseases are commonly used by patients with UC, and can include antihypertensives and other cardiovascular agents, antidiabetics, hormone replacement therapies, medications for gastrointestinal diseases, respiratory agents, and analgesics.

According to longitudinal population based cohort studies, the majority of patients with UC have a mild to moderate course, generally most active at diagnosis and then in varying periods of remission or mild activity; about 14 to 17% of patients may experience an aggressive course. Almost 50% of UC patients have a UC-related hospitalisation at some point during the disease course, and among those hospitalised once, the 5-year risk of re-hospitalisation is about 50%. Consistent predictors of an aggressive UC disease course and colectomy are young age at

diagnosis (<40 years), extensive disease, severe endoscopic activity (presence of deep ulcers), presence of extraintestinal manifestations, early need for corticosteroids, and elevated inflammatory markers (Singh et al. 2019).

Advances in medical therapy have allowed UC to be treated more effectively, and thereby decreased the surgical rates. However, 10% of UC patients will require surgery within the first year of diagnosis and up to 30% will require surgical intervention in their lifetime. The most commonly performed surgery for UC is restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) (Gajendran et al. 2019). Patients with elderly-onset (≥65 years of age) UC were significantly more likely to undergo disease-related surgery than those diagnosed as young adults (between18 and 40 years of age) (adjusted hazard ratio, 1.34; 95% CI, 1.16-1.55) (Nguyen et al. 2017).

UC has not been associated with increased mortality compared with the general population. When assessing the specific causes of death, UC may be associated with an increase in the risk of gastrointestinal-related mortality, which is partly attributed to increased mortality from liver diseases. Additionally, UC may be associated with an inconsistent increase in risk of colorectal cancer (CRC)-related mortality, and respiratory-related mortality (primarily due to asthma-related deaths), despite a decrease in risk of respiratory tract cancers. Overall, there has been no increase in risk of cancer-related or cardiovascular mortality (Fumery et al. 2018). Common causes of death among UC patients include surgical or postoperative complications (mean 44%, range 17-100%) and CRC (mean 37%, range 24-44%), (Jess et al. 2013).

Besides significantly impacting quality of life and work productivity due to debilitating symptoms, UC may also be associated with extraintestinal manifestations including musculoskeletal, pulmonary, cardiac, ocular, and dermatologic disorders. Extraintestinal manifestations are estimated to occur in 21 to 47% of patients with IBD. The extraintestinal manifestations involve multiple organ systems throughout the body; those involving the skin, eyes, and joints usually parallel the degree of intestinal inflammation, but others, involving hepatobiliary and cardiothoracic disorders, typically do not correspond to the degree of intestinal inflammation (Olpin et al. 2017).

UC is also associated with an increased risk of CRC (Singh et al. 2019). Men with UC were at higher risk of CRC (standardised incidence ratio, 2.6; 95% CI, 2.2-3.0) compared with women (standardised incidence ratio, 1.9; 95% CI, 1.5-2.3) (Jess et al. 2012). Overall, the total lifetime risk of CRC in Norwegian patients with UC was 2.3%, which was slightly lower than the cumulative risk of sporadic CRC in Norway. However, patients older than 70 years of age were at 15 times greater risk of CRC compared with those younger than 40 years of age (hazard ratio, 15.68; 95% CI, 1.31-187.92) (Klepp et al. 2020). Chronic inflammation, immunosuppressive therapy, poor disease management, and frequent nonresponse to current therapy among UC patients may play important roles in the increased risk of CRC (Rutter et al. 2004; Velayos et al. 2006). However, the risk of CRC in UC patients has declined over time, partially due to better control of inflammation and surveillance with colonoscopy (Beaugerie and Itzkowitz 2015).

Increased rates of fracture have been described in UC patients with incidence rates ranging from 0.33 to 3.82 per 100 patient-years (Loftus et al. 2003; Ahn et al. 2022). A systematic literature review/meta-analysis found the UC population to have a 1.24 times greater risk of any fracture

compared to the general population (95% CI: 1.04–1.48) (Szafors et al. 2018). Similarly, a systematic literature review/meta-analysis found increased pooled odds of any fracture (OR: 1.25, 95% CI: 0.65–2.43), as well as increased risk of vertebral (OR: 1.99, 95% CI: 0.90–4.42) and hip fractures (OR: 5.07, 95% CI: 0.59–43.72) compared to the general population (Komaki et al. 2019).

UC is frequently associated with manifestations and comorbidities that can affect almost any organ system. Some of these disorders are chronic autoimmune diseases that impact other organ systems, while others are common diseases in other organs that occur with increased frequency in persons with UC (Bernstein et al. 2019; Kim and Cheon 2020). Important comorbidities include:

- Cardiovascular disorders (e.g. VTE, arthrosclerosis, arterial thromboembolic diseases, and myocardial infarction)
- Musculoskeletal disorders (e.g. arthritis)
- Hepatic disorders (e.g. hepatic steatosis, and primary sclerosing cholangitis)
- Obesity
- Type 2 diabetes
- Malignancy (e.g. CRC)
- Respiratory disorders (e.g. parenchymal lung disease, chronic obstructive pulmonary disease, asthma)
- Erythema nodosum
- Uveitis
- Nephrolithiasis
- Infections (e.g. intestinal infections, opportunistic infections, periodontitis)
- Psychiatric disorders (e.g. anxiety, bipolar disorder, depression)

(Román and Muñoz 2011; Andrade et al. 2018; Barber et al. 2018; Bernstein et al. 2018; Bhamre et al. 2018; Kuenzig et al. 2018; Annese 2019; She et al. 2020; Gill et al. 2021)

PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 Toxicity

SII.1.1 Repeat DoseToxicity

A comprehensive toxicology program has been conducted with filgotinib and its major metabolite, GS-829845. This program includes GLP oral repeat-dose toxicity studies of up to 26 weeks duration in the rat and 39 weeks in the dog.

Rat incisor teeth (continually growing teeth) were identified as a target organ for filgotinib, but not the metabolite. Adverse changes were seen macroscopically in the incisor teeth; however, the absence of similar macroscopic changes in molars suggest that these lesions are specific to continuously growing teeth and likely irrelevant for human adults. The safety margin was 4-fold for the human dose of 200 mg q.d. A definitive juvenile rat toxicity study, including 13 weeks of

dosing at exposure margins up to 3.5-fold the human dose of 200 mg q.d., confirmed that there were no effects on teeth that were of clinical significance to human adults.

Additional toxicology studies were conducted and include local tolerance (eye/skin irritation, skin sensitisation) and phototoxicity studies.

The findings in rat incisors are not considered relevant to human adult use. Other than the reproductive/ developmental toxicity listed below, there were no other specific concerns raised by toxicity studies.

SII.1.2 Genotoxicity

A program of in vitro and in vivo genetic toxicology studies was conducted. Filgotinib and its active metabolite GS-829845 were non-genotoxic when evaluated in the bacterial mutagenicity assay, the in vitro mouse lymphoma mutagenicity assay, and the rat bone marrow micronucleus assay.

There were no specific concerns raised by genotoxicity studies.

SII.1.3 Carcinogenicity

A 6-month carcinogenicity study in transgenic mice and a 2-year rat oral carcinogenicity study were conducted. In the 2-year oral carcinogenicity study in Sprague-Dawley rats, there was an increased incidence of benign Leydig cell tumors in male rats treated with filgotinib. However, Leydig cell tumors associated with high dose filgotinib are specific to rats and do not indicate a cancer risk to humans (Chapin et al. 2017). There was no increase in neoplastic findings following administration of the active metabolite GS-829845.

There were no specific concerns raised by carcinogenicity studies.

SII.1.4 Reproductive/Developmental Toxicity

Reproductive toxicology studies in rats and rabbits were conducted. Non-clinical findings of embryolethality and teratogenicity were seen in the non-clinical program at exposures slightly higher than the human dose of 200 mg q.d.

Embryo-fetal development studies were conducted in rats and rabbits. Visceral and skeletal malformations and/or variations were observed at all dose levels of filgotinib and its active metabolite GS-829845.

Filgotinib-related findings were observed in the male reproductive system of both rats and dogs, including dose-dependent impairment of spermatogenesis demonstrated by cessation of sperm production, loss of spermatids, and seminiferous atrophy. Hormonal changes included increased follicle stimulating hormone (FSH) and luteinizing hormone (LH), and decreased inhibin B and testosterone in rats.

At the no observed adverse effect levels (NOAELs) in dogs (the most sensitive species), the exposure margin is 2.7-fold at the 200 mg q.d. dose in humans. Spermatogenic and

histopathological effects were reversible at lower exposures and were not fully reversible at exposure margins of approximately 7 to 9-fold the exposure at the 200 mg q.d. dose in humans.

Reductions in fertility in the presence of severe testicular effects and a near-complete absence of motile or morphological normal sperm were observed in male rats at exposure levels approximately 7.3-fold the 200 mg q.d. dose in humans. No effect on fertility was observed at lower exposure levels, approximately 3.6-fold, even when reductions in sperm motility and morphology were present.

No testicular toxicity was noted following administration of the active metabolite, GS-829845.

The clinical relevance of these non-clinical observations related to testicular function were studied in 2 dedicated PASS (the MANTA and MANTA-RAY trials), which concluded there is no clinically relevant effect on humans.

Embryolethality and teratogenicity is defined as an Important potential risk, and filgotinib is contraindicated during pregnancy.

SII.2 Safety Pharmacology

Filgotinib and GS-829845 had no effects on the respiratory or central nervous system up to 40- and 5-fold, respectively, of the human exposure in subjects with RA at 200 mg filgotinib once daily. Filgotinib and GS-829845 had no relevant effects on cardiovascular parameters (hERG and dog telemetry studies), apart from a slight nonadverse increase in heart rate and arterial pressure with GS-829845 at exposures that were at least 7-fold that of the C_{max} in subjects with RA who received 200-mg filgotinib once daily. There were no relevant effects on ECG and QT interval.

No concerns have been raised by safety pharmacology studies.

SII.3 Metabolism Studies

Filgotinib and GS-829845 (both at 1 μM) were found to be substrates for P-gp based on observed changes in efflux in P-gp over-expressing cells compared to non-transfected cells. Consistent with a P-gp substrate, the efflux ratios of filgotinib and GS-829845 were decreased with P-gp inhibitor cyclosporin A (CsA, 10 mM) in P-gp over-expressing cells. GS-829845, but not filgotinib was found to be a substrate for breast cancer resistance protein (BCRP) based on observed changes in efflux in BCRP over-expressing cells compared to non-transfected cells.

GS-829845 showed no concentration dependent inhibition of P-gp and BCRP mediated transport in vitro up to 400 μM. Thus, no clinical drug interactions with substrates of P-gp and BCRP are anticipated.

Filgotinib and GS-829845 did not inhibit or induce most enzymes or transporters commonly involved with drug interaction such as CYPs or UGTs. In vitro studies are inconclusive regarding the potential of filgotinib to induce CYP2B6 or CYP1A2.

Inhibitors of the P-gp transporter may lead to higher serum concentrations of filgotinib. This could potentially lead to an exaggerated pharmacological or toxic response (theoretical consideration only).

PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

The tables in this section present exposure data to filgotinib for ongoing blinded studies and completed or open-label studies cumulative for all indications and separately for subjects in studies for RA and for UC from the following studies, with a data cut-off of 23 September 2023:

Completed studies at the time of data cut-off:

- Cumulative for all indications:
  - GLPG0634-CL-101, GLPG0634-CL-102, GLPG0634-CL-103, GLPG0634-CL-104, GLPG0634-CL-105, GLPG0634-CL-106, GLPG0634-CL-107, GLPG0634-CL-110, GLPG0634-CL-201, GLPG0634-CL-202, GLPG0634-CL-203, GLPG0634-CL-204, GLPG0634-CL-205, GLPG0634-CL-211, GLPG0634-CL-223, GLPG0634-CL-224, GLPG0634-CL-225, GLPG0634-CL-227, GS-US-379-1582, GS-US-417-0301, GS-US-417-0302, GS-US-417-0303, GS-US-417-3900, GS-US-417-3911, GS-US-417-3916, GS-US-417-4048, GS-US-417-4107, GS-US-417-5937, GS-US-418-3898, GS-US-419-3895, GS-US-419-4015, GS-US-419-4016, GS-US-431-4566, GS-US-431-4567, GS-US-432-4097, GS-US-436-4092, GS-US-437-4093, GS-US-445-4189.
- RA:
  - GLPG0634-CL-201, GLPG0634-CL-202, GLPG0634-CL-203, GLPG0634-CL-204, GLPG0634-CL-205, GLPG0634-CL-227, GS-US-379-1582, GS-US-417-0301, GS-US-417-0302, GS-US-417-0303.
- UC:
  - GS-US-418-3898

Blinded studies ongoing at the time of the data cut-off:

- Cumulative for all indications:
  - GLPG0634-CL-336, GLPG0634-CL-341, GS-US-418-4279
- RA:
  - NA
- UC:
  - GLPG0634-CL-341, GS-US-418-4279

Open-label studies ongoing at the time of the data cut-off:

- Cumulative for all indications:
  - GS-US-417-0304, GS-US-418-3899, GS-US-419-3896
- RA:
  - GS-US-417-0304

– UC:
  - GS-US-418-3899

Table 4: Duration of Exposure to Filgotinib

Duration of exposure	Ongoing Blinded Studies		Completed or Open-Label Studies	
	N	Person-Years	N	Person-Years
Cumulative for all indications				
>= 1 Day	311	426.4	7720	21940.3
> 30 Days	216	422.2	7005	21915.3
> 90 Days	164	415.3	6364	21791.3
> 180 Days	148	410.1	5633	21517.6
> 365 Days	119	390.8	4904	20967.4
> 730 Days	90	353.5	4166	19903.2
> 1095 Days	77	321.6	3555	18371.2
> 1460 Days	40	191.2	2781	15676.2
> 1825 Days	14	78.1	2029	12245.4
> 2190 Days	1	6.1	702	4899.6
Rheumatoid Arthritis				
>= 1 Day	0	0	4174	15938.2
> 30 Days	0	0	4001	15927.8
> 90 Days	0	0	3867	15902.5
> 180 Days	0	0	3601	15803.0
> 365 Days	0	0	3317	15592.7
> 730 Days	0	0	2991	15117.5
> 1095 Days	0	0	2631	14207.0
> 1460 Days	0	0	2182	12658.4
> 1825 Days	0	0	1725	10567.2
> 2190 Days	0	0	673	4718.9
Ulcerative Colitis				
>= 1 Day	150	395.1	1231	3342.8
> 30 Days	150	395.1	1189	3340.9
> 90 Days	147	394.6	1017	3306.4
> 180 Days	138	391.6	933	3273.7
> 365 Days	112	373.9	797	3172.0
> 730 Days	85	338.8	667	2988.3
> 1095 Days	74	312.0	583	2776.7
> 1460 Days	40	191.2	453	2315.5

Duration of exposure	Ongoing Blinded Studies		Completed or Open-Label Studies	
	N	Person-Years	N	Person-Years
> 1825 Days	14	78.1	249	1383.5
> 2190 Days	1	6.1	28	174.7

Duration of Exposure = Last dose date – First dose date + 1.
Person-years was defined as the number of years that each subject was on filgotinib or blinded treatment for ongoing blinded studies.
Ongoing blinded studies included all subjects enrolled in the study and entered in the clinical database at the time of data cut-off date.
Studies with finalized database available were considered completed.
Data cut-off (23 September 2023): GS-US-418-4279, GS-US-417-0304, GS-US-418-3899, GLPG0634-CL-336, GLPG0634-CL-341, GS-US-419-3896 for all indications, GS-US-417-0304 for RA, and GS-US-418-4279, GS-US-418-3899, GLPG0634-CL-341 for UC.

Table 5: Exposure by Age Group and Gender

Age Group	Ongoing Blinded Studies		Completed or Open-Label Studies	
	N	Person-Years	N	Person-Years
Cumulative for all indications				
Male				
<18	0	0	1	0.4
18 - 30	75	70.9	473	760.2
31 - 40	91	148.0	502	1103.9
41 - 50	59	88.9	600	1480.4
51 - 65	34	44.2	852	2347.6
66 - 75	2	0.4	242	662.1
76 - 85	0	0	41	90.1
Female				
18 - 30	5	5.0	665	1358.6
31 - 40	7	0.4	801	2292.8
41 - 50	19	25.9	1115	3583.6
51 - 65	17	37.4	1813	6278.9
66 - 75	2	5.3	521	1682.0
76 - 85	0	0	93	296.7
>85	0	0	1	2.9
Rheumatoid Arthritis				
Male				
<18	0	0	0	0
18 - 30	0	0	36	94.7
31 - 40	0	0	101	380.1
41 - 50	0	0	179	712.5
51 - 65	0	0	383	1469.4
66 - 75	0	0	131	460.4
76 - 85	0	0	30	89.8
Female				
18 - 30	0	0	201	721.8

Age Group	Ongoing Blinded Studies		Completed or Open-Label Studies	
	N	Person-Years	N	Person-Years
31 - 40	0	0	406	1634.7
41 - 50	0	0	728	2907.8
51 - 65	0	0	1439	5616.0
66 - 75	0	0	450	1551.7
76 - 85	0	0	89	296.6
>85	0	0	1	2.9
Ulcerative Colitis				
Male				
<18	0	0	0	0
18 - 30	42	61.0	150	344.3
31 - 40	51	137.9	151	417.0
41 - 50	32	83.0	175	495.7
51 - 65	11	41.8	205	538.5
66 - 75	0	0	46	129.9
76 - 85	0	0	0	0
Female				
18 - 30	1	4.8	138	334.5
31 - 40	0	0	128	349.5
41 - 50	5	24.9	110	354.8
51 - 65	7	36.6	110	316.2
66 - 75	1	5.2	18	62.2
76 - 85	0	0	0	0
>85	0	0	0	0

Duration of Exposure = Last dose date – First dose date + 1.
Person-years was defined as the number of years that each subject was on filgotinib or blinded treatment for ongoing blinded studies.
Ongoing blinded studies included all subjects enrolled in the study and entered in the clinical database at the time of data cut-off date.
Studies with finalized database available were considered completed.
Data cut-off (23 September 2023): GS-US-418-4279, GS-US-417-0304, GS-US-418-3899, GLPG0634-CL-336, GLPG0634-CL-341, GS-US-419-3896 for all indications, GS-US-417-0304 for RA, and GS-US-418-4279, GS-US-418-3899, GLPG0634-CL-341 for UC.

Table 6: Exposure by Dose

Dose	Patients (N)	Patient-time (Person-years)
Cumulative for all indications		
100 mg daily	2462	3108.41
200 mg daily	4509	7233.92
Blinded	1479	705.3
Others	629	1094.15
Total*	**7661**	**12,141.76**
Rheumatoid arthritis		
100 mg daily	1600	1475.16
200 mg daily	2260	3463.35
Blinded	0	-
Others	533	1036.88
Total*	**4033**	**5975.38**
Ulcerative colitis		
100 mg daily	583	360.01
200 mg daily	971	1207.4
Blinded	0	0
Others	0	0
Total*	**1253**	**1567.41**

Duration of Exposure = Last dose date - First dose date + 1.

Person-years was defined as the number of years that each subject was on filgotinib or blinded treatment for ongoing blinded studies. Cumulative exposure cut-off date for ongoing Study GS-US-418-3899 is 28 February 2020; for all other ongoing studies, the data cut-off date is 01 May 2020. All indications included in the cumulative exposure are: RA, CD, UC, PsA, AS, LMN, SjS, CLE, Uveitis, and healthy subjects. RA exposure (presented separately) is cumulative to 24 September 2019, except Study GS-US-417-0304 (12 March 2019) and Study GLPG0634-CL-205 (30 May 2018). UC exposure is based on completed Study GS-US-418-3898 and ongoing Study GS-US-418-3899 (cut-off date 28 February 2020). Subjects who received multiple dosing regimen of filgotinib are counted under each dose group respectively. Others include dose other than 100 mg daily and 200 mg daily. *The total number of subjects is the number of unique subjects, and the sub-categories do not necessarily add up to the total. Exposure to filgotinib from the Phase 2 testicular safety studies (GLPG0634-CL-228 and GLPG0634-CL-227) is included in "Cumulative exposure for all indications", but not in the subsections presenting exposure for subjects with RA or UC separately.

Table 7: Exposure by Ethnic Origin

Ethnic Origin	Ongoing Blinded Studies		Completed or Open-Label Studies	
	N	Person-Years	N	Person-Years
Cumulative for all indications				
White	207	227.3	5680	15841.0
Black or african american	1	0.5	273	426.6
Asian	92	183.0	1171	3833.9
American indian or alaska native	2	4.6	207	581.0
Native hawaiian or other pacific islander	0	0	8	19.7
Multiple	5	0.9	0	0
Other	0	0	280	1044.6
Missing	1	0.1	0	0
Not permitted	3	9.9	101	193.4
Rheumatoid Arthritis				
White	0	0	2949	11377.9
Black or african american	0	0	117	323.8
Asian	0	0	656	2617.5
American indian or alaska native	0	0	204	572.3
Native hawaiian or other pacific islander	0	0	5	16.0
Multiple	0	0	0	0
Other	0	0	240	1011.9
Missing	0	0	0	0
Not permitted	0	0	3	18.8
Ulcerative Colitis				
White	70	200.7	874	2345.5
Black or african american	1	0.5	18	42.1
Asian	75	180.0	290	833.5
American indian or alaska native	2	4.6	1	3.6
Native hawaiian or other pacific islander	0	0	0	0
Multiple	0	0	0	0
Other	0	0	3	6.7

Ethnic Origin	Ongoing Blinded Studies		Completed or Open-Label Studies	
	N	Person-Years	N	Person-Years
Missing	0	0	0	0
Not permitted	2	9.3	45	111.5

Duration of Exposure = Last dose date – First dose date + 1.
Person-years was defined as the number of years that each subject was on filgotinib or blinded treatment for ongoing blinded studies.
Ongoing blinded studies included all subjects enrolled in the study and entered in the clinical database at the time of data cut-off date.
Studies with finalized database available were considered completed.
Data cut-off (23 September 2023): GS-US-418-4279, GS-US-417-0304, GS-US-418-3899, GLPG0634-CL-336, GLPG0634-CL-341, GS-US-419-3896 for all indications, GS-US-417-0304 for RA, and GS-US-418-4279, GS-US-418-3899, GLPG0634-CL-341 for UC.

PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 8: Important Exclusion Criteria in Pivotal Studies in the Development Programme

Criterion	Reason for Exclusion	Considered to be Missing Information
RA: History of or current moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), or within the last 6 months, a cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia, new or significant ECG finding at screening, or any other cardiovascular condition which, in the opinion of the investigator, would put the subject at risk by participation in the study.	As the RA population is at higher risk of cardiovascular (CV) disease, subjects with the most severe CV disease were excluded until the safety profile of filgotinib was more established. Additionally, the active comparator in the Finch trials is contraindicated in NYHA class III/V heart failure.	No Rationale: Although major cardiovascular adverse events (MACE) have been observed in the filgotinib clinical trial program, there have been no signals associated with heart failure, arrhythmias or MACE. The filgotinib safety profile in patients with compensated heart failure, arrhythmias or MACE is not expected to be different to that in subjects with normal cardiac function.
RA: History of malignancy within the past 5 years prior to screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ, with no evidence of recurrence) or lymphoproliferative disease.	Patients with RA and UC are at higher risk of malignancy. Subjects with recent history of malignancy or any lymphoproliferative disease were excluded until the safety profile of filgotinib was established. Drugs with immunosuppressive activity may have the potential to affect host	No Rationale: Patients with history of malignancy are included in the important potential risk of malignancy.

Criterion	Reason for Exclusion	Considered to be Missing Information
UC: History of malignancy in the last 5 years except for subjects who have been successfully treated for non-melanoma skin cancer (NMSC) or cervical carcinoma in situ. History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma.	defenses against malignancies, and the adequacy of previous treatment can be difficult to determine. Thus, exclusion of subjects with known previous malignancy was prudent while data was generated on the incidences and types of malignancies observed in patients treated with filgotinib.	
RA: History of gastrointestinal (GI) perforation	GI perforations have been seen in studies with other JAK inhibitors. Subjects with history of GI perforation were excluded until the safety profile of filgotinib was established.	No Rationale: Patients with history of GI perforation are included in the important potential risk of GI perforation.
RA: History of organ or bone marrow transplant Positive serology for human immunodeficiency virus (HIV) 1 or 2	Subjects with immunodeficiency were excluded from clinical trials until the safety profile was more established.	No Rationale: Development of infection (including serious and opportunistic infections) is the main risk of immunomodulatory therapy in this patient population. Serious and opportunistic infections is an Important identified risk for filgotinib.
Evidence of active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection.	As there is an increased risk of viral reactivation in subjects receiving an immunomodulatory therapy, subjects with evidence of active HCV or HBV infection were excluded from clinical trials until the safety profile was established.	Yes
RA: Patients with history of/ concurrent/ recurrent or chronic infections. UC: History of opportunistic infection or immunodeficiency syndrome, and subject currently on any chronic systemic (oral or intravenous) anti-infective therapy for chronic infection (such as pneumocystis (PCP), cytomegalovirus (CMV), herpes zoster, atypical	As there is an increased risk of infection for RA and UC subjects receiving an immunomodulatory therapy, subjects with history of/ concurrent/ recurrent or chronic infections were excluded from clinical trials until the safety profile was established.	No Rationale: The SmPC contains guidance in Section 4.4 to consider risks and benefits when prescribing to patients with history of, or risk factors for, serious, chronic, recurrent or opportunistic infections, and advice on when to consider treatment interruption.

Criterion	Reason for Exclusion	Considered to be Missing Information
mycobacteria). History of disseminated Staphylococcus aureus.		
Significant blood loss (>450 mL) or transfusion of any blood product within 12 weeks prior to Day 1. UC: History of major surgery or trauma within 30 days prior to screening.	To ensure clinical trial subjects were able to provide blood samples as required in the protocol.	No Rationale: This is as exclusion criteria specific to clinical trials and is not applicable to everyday practice. Possible consequences of major trauma or surgery such as low hemoglobin secondary to blood loss or infection are included in the Sections 4.2 and 4.4 of the SmPC.
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥1.5x ULN;	Raised transaminases have been seen in studies with other JAK inhibitors. Subjects with raised transaminases were excluded until the safety profile of filgotinib was more established, in case the raised transaminases were exacerbated.	No Rationale: There has been no evidence of an effect on transaminases in the clinical trial program. There are no different risks expected in this population.
Total bilirubin level ≥2x ULN unless the subject has been diagnosed with Gilbert's disease and this is clearly documented.	Safety profile in patients with hepatic impairment had not been studied and was therefore not recommended for use in these patients.	No Rationale: Study GS-US-417-4048 in mild or moderate hepatically impaired subjects (Child-Pugh A or B) has demonstrated dose adjustment is not necessary, and filgotinib is well tolerated.
Estimated creatinine clearance <40 mL/min based on the Cockcroft Gault formula.	Safety profile in patients with severe renal impairment had not been established in the filgotinib clinical trials.	No Rationale: Study GLPG0634-CL-106 included subjects with severe renal impairment and concluded that filgotinib was well tolerated in these subjects. Decreased renal clearance in these subjects led to a 45% increase in plasma exposure. This could result in subjects with severe renal impairment having plasma levels equivalent to a 300 mg filgotinib tablet, when taking a 200 mg tablet. Study GLPG0634-CL-102 showed 300 mg q.d. filgotinib to be well tolerated in healthy subjects when taken daily for a period of 10 days. A dose of 100 mg once daily is recommended for patients with moderate or severe renal impairment (eGFR 15 to <60 mL/min). Filgotinib has not been studied in patients with end stage renal disease (eGFR <15 mL/min) and is therefore not recommended for use in these patients.
Administration of a live/attenuated vaccine	There is a potential risk of primary infection following administration	No Rationale: Section 4.4 of the SmPC recommends that live vaccines are not administered during, or

Criterion	Reason for Exclusion	Considered to be Missing Information
within 30 days prior to Day 1 or planned during the study.	of live/ attenuated vaccine.	immediately prior to, filgotinib treatment. Section 4.4 recommends that immunisations are updated according to current immunisation guidelines prior to initiating filgotinib treatment.
Subjects receiving vaccines during treatment with filgotinib.	There are no available data on the concurrent use of filgotinib and vaccine efficacy.	Yes
History of treatment with lymphocyte-depleting therapies, including but not limited to alemtuzumab, cyclophosphamide, total lymphoid irradiation, and rituximab. History of cytapheresis ≤2 months prior to screening.	These agents have a long-term immunosuppressive or other known or unknown effects that could put patients in clinical studies receiving filgotinib at higher risk for adverse effects or otherwise affect study result interpretation.	No Rationale: Section 4.4 of the SmPC states that combination of filgotinib with other potent oral immunosuppressants such as ciclosporin, tacrolimus, biologics or other JAK inhibitors is not recommended as a risk of additive immunosuppression cannot be excluded.
Any chronic medical condition (including, but not limited to, cardiac or pulmonary disease, or substance abuse) or psychiatric problem that, in the opinion of the Investigator or Sponsor, would make the subject unsuitable for the study or would prevent compliance with the study protocol procedures.	To ensure subjects are able to participate in the clinical trial procedures.	No Rationale: Although the risk of CV disease is less pronounced in subjects with UC compared with RA, subjects with any chronic medical condition including cardiac, that, in the opinion of the Investigator or Sponsor, would make the subject unsuitable for the study were excluded until the safety profile was more established. Cardiovascular events have been observed in the filgotinib clinical trial program, however, the numbers were small and there have been no signals associated with heart failure, arrhythmias, or MACE. The filgotinib safety profile in patients with compensated heart failure, arrhythmias or MACE is not expected to be different to that in subjects with normal cardiac function. Patients with other chronic conditions are not expected to have a different safety profile from other patients with UC.
Active tuberculosis (TB) or history of latent TB that has not been treated	As there is an increased risk of opportunistic infection including TB as well as viral or other pathogen reactivation in subjects receiving immunomodulatory therapy.	No Rationale: Opportunistic infections (including TB) is an important identified risk. Section 4.4 of the SmPC recommends screening for TB, initiating antimycobacterial therapy in patients with latent TB before administering filgotinib, and not to administer filgotinib to patients with active TB. The Warnings and Precaution section also recommends that patients are monitored for signs and symptoms of TB, including patients who tested negative for latent TB prior to initiating treatment.

Criterion	Reason for Exclusion	Considered to be Missing Information
History of symptomatic herpes zoster (HZ) or herpes simplex within 12 weeks of screening, or any history of disseminated herpes simplex, disseminated herpes zoster, ophthalmic zoster, or central nervous system zoster.	Patients with recurrent or complicated HZ may be at increased risk for reactivation.	No Rationale: HZ is an adverse drug reaction (ADR) in the Jyseleca SmPC and is an important identified risk in the Jyseleca EU-RMP.
Subjects with UC aged 75 years and over	The safety profile of filgotinib in this age group has not been established at the time of study onset.	No Rationale: Patients 75 years and older are not included in the indication for UC. Section 4.2 of the SmPC states that filgotinib is not recommended in patients with UC aged 75 years and older, as there is no data in this population.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

In the RA program, 4033 subjects with moderately to severely active RA have been exposed to filgotinib in the clinical trial program. In the UC program, 1253 subjects with moderately to severely active UC have been exposed to filgotinib in the clinical trial program.

The RA clinical trial population is large enough to detect at least some rare ADRs. ADRs with a frequency greater than 1 in 1344 could be detected if there were no background incidence. The UC clinical trial population is large enough to detect at least some uncommon ADRs. ADRs with a frequency greater than 1 in 418 (0.2%) could be detected in the UC program if there were no background incidence.

In the RA program, 2402 subjects with moderately to severely active RA have been exposed to filgotinib for more than 1 year, and 495 for more than 3 years in the clinical trial program. In the UC program, 797 subjects with moderately to severely active UC have been exposed to filgotinib for more than 1 year, and 229 for more than 2 years.

No ADRs specifically associated with prolonged exposure to filgotinib have been identified in the filgotinib RA and UC clinical trial programs. The sponsor is conducting long-term safety clinical trials.

No cumulative effects related to filgotinib have been identified in the filgotinib clinical trial program. The sponsor is conducting long-term safety clinical trials.

No ADRs for filgotinib with a long latency have been identified in the filgotinib RA or UC clinical trial program. The sponsor is conducting long-term safety trials in RA and UC.

SIV.3 Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programmes

Table 9: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure (Number of Subjects and Patient-Years)	Associated With a Safety Specification
Pregnant women	Cumulatively to 31 March 2020, there were 23 first trimester exposures in study subjects receiving filgotinib in the filgotinib development program in RA and UC indications: 19 pregnancies in subjects with RA and 4 pregnancies in study subjects with UC. The outcomes of the pregnancies were 7 spontaneous abortions, 3 elective abortions, 2 ectopic pregnancies, and 9 live births. Additionally, pregnancy outcomes are pending for 2 cases. Of the 9 live births, 1 case, for a subject with RA, reported a congenital abnormality (Pentalogy of Fallot).	No Rationale: Filgotinib is contraindicated in pregnancy.
Breastfeeding women	Not included in the clinical development program.	No Rationale: SmPC Section 4.6 advises against use of filgotinib during breast feeding. In animal studies, filgotinib was detected in the plasma of nursing rat pups likely due to the presence of filgotinib in milk. It is not known if filgotinib is excreted in human milk. Safety profile in infants is not known.
Patients with relevant comorbidities:		
– Patients with hepatic impairment	In Study GS-US-417-4048 thirty subjects with mild or moderate hepatic impairment (10 in each group) were exposed to a single 100 mg filgotinib dose.	No Rationale: Study GS-US-417-4048 in mild or moderate hepatic impaired subjects has demonstrated that the pharmacokinetics are unchanged and therefore a dose adjustment is not necessary.
– Patients with renal impairment	In Study GLPG0634-CL-106 fifteen subjects with renal impairment (3 with severe and 6 each with mild or moderate renal impairment) were exposed to 100 mg filgotinib daily dosing for 10 days. Filgotinib has not been studied in patients with end stage renal disease (eGFR <15 mL/min).	No Rationale: In Study GLPG0634-CL-106 no accumulation of filgotinib was observed, which is consistent with filgotinib short apparent terminal half-life (5.42-10.9 hours). Renal clearance decreased with the degree of renal impairment leading to 45% increase in filgotinib plasma exposure ($AUC_{0\text{-}24h}$) in

		subjects with severe renal impairment. A dose of 100 mg q.d. is recommended for subjects with moderate or severe renal impairment (eGFR 15 to <60 mL/min).
– RA: Patients with other relevant comorbidities such as cardiovascular impairment	Patients with moderate to severe congestive heart failure (NYHA III or IV) were not included in the clinical development program.	No Rationale: No signals associated with heart failure, arrhythmias or MACE have been observed in the filgotinib clinical trial program. The filgotinib safety profile in patients with compensated congestive heart failure, arrhythmias or MACE is not expected to be different to that in subjects with normal cardiac function.
– Immuno-compromised patients	Not included in the clinical development program.	No Rationale: The occurrence of serious and opportunistic infections, is a concern for immunomodulating drugs like filgotinib in this patient population and is included as an Important identified risk for filgotinib.
– Patients with a disease severity different from inclusion criteria in clinical trials	RA: While active disease was required at entry to trial, many subjects achieved remission after entry to trial, therefore information is available on a wide array of disease activity. UC: Patients with moderately to severely active UC (as determined by a centrally read endoscopy score ≥2, a rectal bleeding score ≥1, a stool frequency score ≥ 1 and physician global assessment (PGA) of ≥2 as determined by the Mayo clinic scoring system with endoscopy occurring screening; total score must be between 6 and 12, inclusive).	No Rationale: All RA disease severity covered in clinical trial program, therefore no additional concerns. The SmPC states the target population: 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.
Population with relevant different ethnic origin	Patients of different ethnic origin were included in the clinical trial program for filgotinib.	No Rationale: The effect of race in subjects with RA receiving filgotinib was examined by population PK analysis and no impact of race was identified on the PK of filgotinib or its major metabolite.
Subpopulations carrying known and relevant genetic polymorphisms	Not included in the clinical development program.	No Rationale: No relevant subpopulations have been identified in RA or in UC, so there are no additional concerns.
Elderly	RA: As of 24 September 2019, 566 subjects aged 66-75 years were enrolled with 740.37 patient-years of exposure. Study GLPG0634-CL-104 included 10 healthy subjects between 65 and 74 years.	No Rationale: Prevalence of RA is increased in the elderly population and there was no upper age limit in the phase 3 RA program. No additional safety concerns were identified from subjects aged 66 years or older in the RA program. No

	UC: 65 subjects aged 66-75 years were enrolled in the UC studies, with 88.82 patient-year exposure.	safety concerns were raised in subjects aged 66-75 years in the UC program.
Very elderly (>75 years)	RA: As of 24 September 2019, 120 subjects aged >75 years old enrolled, with 150.68 patient-years of exposure. Study GLPG0634-CL-104 included 10 healthy subjects over 75 years. UC: No subjects aged >75 years were included in the UC clinical trials.	Yes RA: Study GLPG0634-CL-104 included healthy subjects over 75 years and concluded that filgotinib was well-tolerated in healthy subjects over 75 years and that there were no clinically relevant changes in filgotinib pharmacokinetics in the elderly. In the RA Phase 3 program there was a higher incidence of serious infections in the very elderly. However, data from very elderly subjects in the Phase 3 program is limited and a starting dose of 100 mg q.d. is recommended. UC: Patients aged 75 years and older are not included in the indication. Section 4.2 of the SmPC states that filgotinib is not recommended in patients with UC aged 75 years and older, as there is no data in this population.

PART II: MODULE SV – POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Jyseleca (filgotinib) received marketing authorisation in the European Union (EU) on 24 September 2020, and in Japan on 25 September 2020. Post-authorisation patient exposure data for Jyseleca will be included in Jyseleca Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Reports (PSUR/PBRERs).

SV.1.1 Method Used to Calculate Exposure

The MAH has provided the cumulative post-marketing patient exposure to marketed Jyseleca based on sales data utilizing defined daily dose method. As it is recommended to take Jyseleca once daily, the estimated patient-years exposure (PYE) calculation is the total number of tablets sold during the reporting interval divided by 365.25. It should be noted that the use of sales data for patient exposure calculations will generally overestimate patient exposure due to the accumulation of drug stocks at pharmacies/distributors.

SV.1.2 Exposure

Based on sales data the cumulative worldwide exposure to Jyseleca was estimated to be 44912 patient-years (PY) with an interval worldwide exposure of 14970 PY. The detailed Jyseleca exposure per country where sales are active and dosing regimen are displayed in Table 10 as follows.

Table 10: Estimated Post-authorisation Exposure to Jyseleca for all Indications

Region	Estimated Patient Exposure (Rounded to Nearest Whole Number)											
	Reporting Interval						Cumulative					
	100 mg		200 mg		Total		100 mg		200 mg		Total	
	Total Tablets	PY	Total Tablets	PY	Total Tablets	PY	Total Tablets	PY	Total Tablets	PY	Total Tablets	PY
Europe												
Austria	CCI											
Belgium	CCI											
Croatia	CCI											
Czech Republic	CCI											
Denmark	CCI											
Finland	CCI											
France	CCI											
Germany	CCI											
Ireland	CCI											
Italy	CCI											
Netherlands	CCI											
Poland	CCI											
Portugal	CCI											
Slovakia	CCI											
Slovenia	CCI											
Spain	CCI											
Sweden	CCI											
EU Total	CCI											
Norway	CCI											
United Kingdom	CCI											
Europe Total	CCI											
Rest of world												
Japan	CCI											
Grand Total	CCI											

EU = European Union; PY = patient-years
United Kingdom includes England, Wales, Scotland, and Northern Ireland.
Ireland refers to the Republic of Ireland.
The PY calculations are rounded to closest whole number.
Data cut-off: 23 September 2023
Reference: filgotinib PSUR 6

PART II: MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for Misuse for Illegal Purposes

There are no data to suggest that there is potential for filgotinib to be misused for illegal purposes.

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 11: Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reason	List of Risks
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	Identified risk of Dizziness. Dizziness is included in the list of ADRs in Section 4.8 of the SmPC. Section 4.7 provides advice on informing patients who drive or use machines. The clinical impact of this risk is considered to be minimal in relation to the severity of the indication treated.
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised)	Identified risks of pneumonia and urinary tract infection, and potential risk of primary infection following administration of live/ attenuated vaccine. Pneumonia and urinary tract infection are included in the list of ADRs in Section 4.8 of the SmPC. Section 4.4 of the SmPC provides advice for monitoring patients with serious infections and consideration for interrupting treatment. Infection-related risks are well known to healthcare professionals who treat RA patients with immunomodulatory drugs. There are no additional pharmacovigilance activities associated with these risks and specific clinical measures to manage infections have become fully integrated into standard clinical practice. Section 4.4 of the SmPC advises against the use of live vaccines during or immediately prior to filgotinib treatment and recommends that immunisations are updated in line with current immunisation guidelines prior to initiating treatment. There are no additional pharmacovigilance activities associated with the risk of primary infection following administration of live/ attenuated vaccine and specific clinical measures to address this risk have become fully integrated into standard clinical practice (Assen et al. 2011). The additional RMMs (Healthcare professional guide and patient alert card [PAC]) provide advice on infections and live/attenuated vaccines.

Reason	List of Risks
Known risks that do not impact the risk-benefit profile	Identified risks of Neutropenia. Neutropenia is included in the list of ADRs in Section 4.8 of the SmPC. An initial decrease in neutrophil counts over the first 4 weeks of treatment was seen in clinical trials in filgotinib-treated subjects. Higher frequencies of ≥ Grade 3 neutropenia were seen for filgotinib-treated subjects compared to those subjects treated with other csDMARDs, MTX or placebo. However, there was no clear association of Grade 3 or 4 neutropenia with infection during the first 12 weeks of treatment, and permanent study drug discontinuation due to neutropenia was infrequent in the pooled Phase 2 and 3 safety population. Neutropenia is associated with other medications used to treat RA, such as other JAK inhibitors, and bDMARDs. Consequently, prescribers are used to managing this risk. The possible consequence of neutropenia, infection, is addressed by the important identified risk of serious and opportunistic infections.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 12: Important Identified Risk, Important Potential Risks and Missing Information

Important Identified Risks	Risk-Benefit Impact
Serious and opportunistic infections	Serious and opportunistic infections have been reported for subjects in RA clinical trials receiving filgotinib. The risk of serious infection is a concern for patients treated with any disease-modifying antirheumatic drug, and the underlying immune pathology and chronic use of drugs such as corticosteroids has also been associated with an increased risk of infection. Serious or opportunistic infections could have an adverse impact on the patient if not managed appropriately. The outcome could be serious, include hospitalisations and possibly be fatal. As this risk is manageable with established medical practice in rheumatology where immunomodulatory drugs are commonly prescribed, the impact of this risk is expected to be low.
Herpes zoster	Herpes zoster has been reported for subjects in RA clinical trials receiving filgotinib. The risk of herpes zoster is increased for patients with RA compared to age matched controls and is a concern for patients treated with any DMARDs. Herpes zoster is a painful and often debilitating condition and could have an adverse impact on the patient if not treated promptly. The outcome could be serious and include hospitalisations, however it is unlikely to be fatal. As this risk is manageable with available treatment and prophylactic vaccination within established medical practice in rheumatology, the impact of this risk is expected to be low.

Important Potential Risks	Risk-Benefit Impact
Embryolethality and teratogenicity	Embryolethality and teratogenicity were identified in non-clinical studies, with teratogenicity observed at exposures slightly higher than those achieved with the human dose of 200 mg q.d. It is not known whether embryolethal and teratogenic effects apply to humans exposed to filgotinib, however, similar effects from non-clinical studies of other medicinal products in the same class have been identified. The possible impact for a pregnant female subject taking filgotinib could be the fetal death, or a congenital anomaly. The possibility of these outcomes could negatively impact the risk-benefit, especially in the predominantly female RA population, if not managed according to labeling information stating that filgotinib is contraindicated in pregnancy and effective contraception should be used. Of note, a common co-medication in RA patients is MTX, which carries the same risk; consequently, the Prescribers are experienced in managing this risk for their female RA patients. As this risk is manageable, and the majority of the female RA population is elderly and no longer of childbearing potential, the impact of this risk is expected to be low.
Impaired spermatogenesis, leading to possible reduction in male fertility	Filgotinib-related findings were observed in the male reproductive system of both rats and dogs, and not all findings were reversible. At the no-observed-adverse-effect levels (NOAELs) in dogs (the most sensitive species), the exposure margin is 2.7-fold at the 200 mg once daily dose in humans. Spermatogenic and histopathological effects were reversible at lower exposures and were not completely reversible at exposure margins of approximately 7 to 9-fold the exposure at the 200 mg once daily dose in humans. If these findings also occur in humans and if they were irreversible, this may have an adverse impact on male patients who have a future reproductive interest. RA is 2 to 3 times less common in men than women. RA in young men is relatively rare, with the highest prevalence in the elderly (>70 years) (Arthritis 2019). As male patients with a reproductive interest are therefore anticipated to be few, the impact of this risk is expected to be low. Furthermore, common co-medications in RA patients include MTX and sulfasalazine, which are associated with impaired spermatogenesis. Inflammatory diseases such as RA can impact spermatogenesis (Azenabor et al. 2015). Therefore, Prescribers are experienced in managing risks associated with male fertility for their RA patients.
Malignancy	There have been no non-clinical findings that are directly relevant to malignancy. However, it is possible that any drug with an immunomodulatory mechanism of action may have an effect on the incidence of malignancies. Patients with RA have an increased risk of malignancy. It is currently unknown if filgotinib increases this risk, or if filgotinib will increase the risk of recurrence of malignancy, or of a secondary malignancy, in this patient population. The incidence of malignancies in the clinical trial program was low and consistent with the rate expected in the population with RA, however clinical trial data are insufficient to assess the incidence of malignancies and long-term safety evaluations of the Phase 2b and 3 clinical trial populations are ongoing. The impact of rare events with a long latency is expected to be low in the context of the morbidity and mortality of the disease treated.

Venous thromboembolism (deep venous thrombosis and pulmonary embolism)	RA patients have an elevated risk of venous thromboembolism (VTE). VTE (deep venous thrombosis and pulmonary embolism) has been reported for subjects in RA clinical trials receiving filgotinib. Deep venous thrombosis (DVT) and pulmonary embolism (PE) can be serious and life-threatening conditions, but there is currently insufficient evidence indicating a causal relationship between filgotinib treatment and DVT/PE occurrence. The exposure-adjusted incidence rate of VTE events in the pooled RA filgotinib data is low and within the background incidence rate of the target population. As this risk is manageable with established medical practice in clinical rheumatology, the impact of the risk is considered to be low in the context of overall burden of the disease treated.
Gastrointestinal (GI) perforation	There have been no non-clinical findings that are directly relevant to gastrointestinal (GI) perforation. GI perforations have been reported in RA, either in association with the disease itself or in association with NSAIDs, glucocorticoids, or other RA therapies. In recent years, reports of GI perforations in association with biologic agents have arisen. In particular, drugs that inhibit the interleukin-6 (IL-6) cytokine receptors have demonstrated a higher risk of perforations compared with other therapies (Jagpal and Curtis 2018). Recent reports suggest that JAK inhibitors may also increase the risk of perforation, perhaps via downstream effects on IL-6 signaling (Migita et al. 2014). Other significant risk factors for GI perforation include a history of diverticulitis, increasing age, and other GI conditions. GI perforations are potentially life-threatening events that warrant prompt medical/surgical intervention. Advanced age and background immunosuppressive medications are common in the moderately to severely active RA population and place this population at increased risk. Data from the filgotinib RA clinical trial program do not support an association of GI perforation with filgotinib. The impact of rare events is expected to be low in the context of the morbidity and mortality of the diseases treated.
Non-melanoma skin cancer (NMSC)	Filgotinib is an immunomodulator that may impact cancer-related immune surveillance. Patients with RA have an increased risk of NMSC. However, it is currently unknown if filgotinib increases this risk. The incidence of NMSC in the filgotinib clinical trial program was lower than the expected rate in the target RA population. However, the clinical trial data are insufficient to assess the incidence of NMSC and long-term safety evaluations of the Phase 2b and 3 clinical trial populations are ongoing. NMSC is usually curable. The impact of NMSC is expected to be low in the context of the morbidity and mortality of the disease treated.
Major adverse cardiovascular events (MACE)	The association of JAK inhibitors and cardiovascular outcomes in the RA population, including the potential for MACE as a result of elevations of lipid levels remains unclear. RA patients have a substantially elevated risk of cardiovascular morbidity and mortality that cannot be entirely explained by traditional CV risk factors, indicating that RA-specific characteristics (systemic inflammation and disease activity) may be associated with this increase in risk (Crowson et al. 2013; Hollan et al. 2015). Traditional CV risk factors (e.g. smoking, dyslipidemia, obesity, hypertension, diabetes mellitus, age and CV history) may also apply to patients with RA. CV disease is a major public health issue and is among the leading causes of morbidity and mortality worldwide (Roth et al. 2017). However, at the low

	rates observed in the filgotinib clinical trial program, the public health impact of MACE is considered to be low.
Hyperlipidemia	Filgotinib treatment was associated with dose-dependent increases in total cholesterol and high-density lipoprotein (HDL) levels, while low density lipoprotein (LDL) levels were slightly increased, and LDL/HDL ratios were generally unchanged. RA itself is an established risk factor for dyslipidemia, with inflammation thought to modify lecithin-cholesterol acyltransferase (LCAT) activity and cholesterol esterification (important in transport of cholesterol). Potentially, JAK inhibitors may reverse this activity by decreasing cholesterol ester catabolism, resulting in increased cholesterol levels (Charles-Schoeman et al. 2015). The outcome of hyperlipidemia can range from mild (requiring medication), to severe due to the potential development of cardiovascular disease. As observed changes in total cholesterol, HDL, and LDL in Phase 3 filgotinib studies were numerically small and the ratio of LDL/HDL were generally unchanged, the impact of this risk is expected to be low.
Varicella zoster	Adult patients receiving immunomodulatory treatment without any evidence of immunity to varicella, may be at increased risk of primary varicella zoster (chicken pox) complications should they contract the virus. This theoretical risk remains poorly characterised as in the filgotinib RA development program as the incidence of primary varicella infection was very low. Primary varicella infection could have an adverse impact on the patient, for example, leading to varicella pneumonia. The outcome of complications could be serious and possibly be fatal. Primary infection in adults is rare as most patients are vaccinated or infected in childhood. With the availability of the vaccine for people with no history of the disease and the widely available post-exposure prophylaxis treatments, the impact of this potential risk is expected to be low.
Missing Information	**Risk-Benefit Impact**
Use in patients with evidence of untreated chronic infection with hepatitis B or C	Subjects with active hepatitis B or hepatitis C disease were excluded from filgotinib clinical trials. Subjects with evidence of prior exposure to hepatitis B (hepatitis B core antibody positive, surface antigen negative and hepatitis B DNA negative) and/or hepatitis C (hepatitis C antibody positive) but without active disease were allowed to enroll in Phase 3 trials, with the requirement to undergo viral load testing every 3 months. It remains unclear whether filgotinib affects hepatitis B and/or hepatitis C viral activity in patients with RA, due to the immunomodulatory potential of JAK inhibitors. Across the clinical development program for filgotinib in RA, a limited number of AEs related to hepatitis B were reported. However, all were asymptomatic viral detections observed during routine monitoring without clinically significant elevations in liver function tests. Exposure-adjusted incidence rates (EAIRs) for AEs associated with potential hepatitis B or hepatitis C infections were similar across treatment groups of all Safety Analysis Sets. The SmPC provides advice in Section 4.4 that screening for viral hepatitis and monitoring for reactivation should be performed before starting and during therapy with filgotinib. The potential impact of this safety concern is considered to be low.
Effect on vaccination efficacy	Subjects who had a live/attenuated vaccination within 30 days prior to Day 1, or planned during the study, were excluded from filgotinib clinical trials. It is unknown if vaccine efficacy will be reduced if given during, or just prior to, filgotinib therapy due to the immunomodulatory potential of

	JAK inhibitors. The impact of reduced vaccine efficacy could be decreased protection from illness in the patient population, for example from annual influenza vaccine. The SmPC recommends that vaccinations are updated in line with local recommendations before treatment with filgotinib is initiated. EULAR provides recommendations on vaccination in adult patients with autoimmune inflammatory rheumatic diseases (Assen et al. 2011) and specific clinical measures to manage vaccination in RA patients have become fully integrated into standard clinical practice. The potential impact of this safety concern is considered to be low.
Use in the very elderly (>75 years)	Elderly RA patients are subject to polypharmacy, usually have more comorbidity and predispose to the development of infections and malignancies particularly after receiving immunosuppressive treatments. Although the number of very elderly subjects (>75 years) exposed to filgotinib was limited in the RA clinical program, no specific signals were identified, and no special concern for drug interaction with filgotinib is raised either in this population. However, there was a higher incidence of serious infections in this population in the Phase 3 program. The SmPC provides advice in Section 4.2 that clinical experience in patients >75 years is limited and a starting dose of 100 mg q.d. is recommended. In the elderly population, an increased risk for serious AEs is observed for the 200 mg than compared to the 100 mg dose. The risks associated with the 200 mg dose vs the 100 mg dose are more pronounced among subjects ≥75 years of age as compared to for subjects <75 years of age. Since both the 100 mg and 200 mg doses of filgotinib have been demonstrated to be effective, the benefits of recommending the 200 mg dose to all elderly patients are not considered to outweigh the risks. Therefore, a starting dose of 100 mg should be recommended if filgotinib is considered for patients aged 75 or above. The potential impact of this safety concern is overall considered to be low.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Upon request of PRAC (EMEA/H/C/PSUSA/00010879/202209), fractures are included as an important potential risk.

SVII.3 Details of Important Identified Risks, Important Potential Risks and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1 Important Identified Risks

SVII.3.1.1.1 Serious and Opportunistic Infections

Potential mechanisms:

The JAK/STAT pathway is involved in the signaling pathway of numerous interferons, interleukins and cytokines that are involved in the immuno-inflammatory response. In addition,

the underlying disease and concomitant use of immunosuppressive therapies increases the risk of infection in RA and UC patients.

Evidence source(s) and strength of evidence:

Serious and opportunistic infections have been reported with the use of other JAK inhibitors and other immunomodulatory drugs used to treat RA and UC, such as TNF inhibitors. Serious infections are considered a class effect of the JAK inhibitors. However, from the pivotal clinical trial data for filgotinib in RA in the Integrated Safety Summary (ISS), the rate of serious infections is lower than that published for biological DMARDS (Strand et al. 2015).

RA: The RA ISS is based on a pooled dataset of Phase 2b and 3 studies in RA of subjects receiving at least 1 dose of filgotinib 100 mg or 200 mg q.d. to support the marketing authorisation application for RA.

UC: The exposure-adjusted incidence rates (EAIRs) of serious or opportunistic infections were low across all treatment groups in the Induction and Maintenance studies.

As patients with RA and patients with UC are at a higher risk of infections, and the use of immunomodulatory therapy a possible contributing factor, serious and opportunistic infections has been classified as an important identified risk warranting further study as specified in the pharmacovigilance (PV) plan of this RMP.

Characterisation of the risk:

Pneumonia is an ADR for filgotinib. Other than pneumonia, exposure-based analysis of the ISSs for RA and for UC has not identified any signals for serious (infection SAEs) or opportunistic infections.

RA: In the pooled data that comprises the ISS for RA, the following rates were seen for the most frequently occurring infection SAEs and opportunistic infection events.

Table 13: EAIRs of Treatment-Emergent Serious Infectious Adverse Events (Occurring in ≥3 Subjects Receiving Filgotinib) by Preferred Term (Safety Analysis Set, As Treated Subjects)

	Filgotinib 200 mg q.d			Filgotinib 100 mg q.d		
Preferred Term	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)
Number (%) of Subjects with Any Treatment-Emergent Serious Infectious Adverse Event	48 (2.6%)	19 (4.2%)	67 (3.0%)	48 (3.2%)	3 (2.0%)	51 (3.1%)
Pneumonia	15 (0.8%)	3 (0.7%)	18 (0.8%)	10 (0.7%)	0	10 (0.6%)
	0.5 (0.3,0.8)	0.3 (0.1,0.8)	0.4 (0.3,0.7)	0.5 (0.2,0.9)	0.0 (0.0,5.4)	0.5 (0.2,0.9)
Cellulitis	4 (0.2%)	0	4 (0.2%)	3 (0.2%)	1 (0.7%)	4 (0.2%)

Preferred Term	Filgotinib 200 mg q.d			Filgotinib 100 mg q.d		
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)
	0.1 (0.0,0.3)	0.0 (0.0,0.4)	0.1 (0.0,0.3)	0.2 (0.0,0.4)	1.5 (0.0,8.2)	0.2 (0.1,0.5)
Bronchitis	2 (0.1%)	1 (0.2%)	3 (0.1%)	3 (0.2%)	0	3 (0.2%)
	0.1 (0.0,0.2)	0.1 (0.0,0.5)	0.1 (0.0,0.2)	0.2 (0.0,0.4)	0.0 (0.0,5.4)	0.1 (0.0,0.4)
Pyelonephritis acute	1 (<0.1%)	1 (0.2%)	2 (<0.1%)	4 (0.3%)	0	4 (0.2%)
	0.0 (0.0,0.2)	0.1 (0.0,0.5)	0.0 (0.0,0.2)	0.2 (0.1,0.5)	0.0 (0.0,5.4)	0.2 (0.1,0.5)
Appendicitis	0	0	0	4 (0.3%)	0	4 (0.2%)
	0.0 (0.0,0.1)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.2 (0.1,0.5)	0.0 (0.0,5.4)	0.2 (0.1,0.5)
Arthritis bacterial	3 (0.2%)	0	3 (0.1%)	0	1 (0.7%)	1 (<0.1%)
	0.1 (0.0,0.3)	0.0 (0.0,0.4)	0.1 (0.0,0.2)	0.0 (0.0,0.2)	1.5 (0.0,8.2)	0.0 (0.0,0.3)
Herpes zoster	2 (0.1%)	1 (0.2%)	3 (0.1%)	1 (<0.1%)	0	1 (<0.1%)
	0.1 (0.0,0.2)	0.1 (0.0,0.5)	0.1 (0.0,0.2)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)
Lower respiratory tract infection	2 (0.1%)	0	2 (<0.1%)	2 (0.1%)	0	2 (0.1%)
	0.1 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.2)	0.1 (0.0,0.4)	0.0 (0.0,5.4)	0.1 (0.0,0.4)
Sepsis	2 (0.1%)	1 (0.2%)	3 (0.1%)	0	0	0
	0.1 (0.0,0.2)	0.1 (0.0,0.5)	0.1 (0.0,0.2)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)
Septic shock	3 (0.2%)	0	3 (0.1%)	1 (<0.1%)	0	1 (<0.1%)
	0.1 (0.0,0.3)	0.0 (0.0,0.4)	0.1 (0.0,0.2)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)
Urinary tract infection	1 (<0.1%)	1 (0.2%)	2 (<0.1%)	2 (0.1%)	0	2 (0.1%)
	0.0 (0.0,0.2)	0.1 (0.0,0.5)	0.0 (0.0,0.2)	0.1 (0.0,0.4)	0.0 (0.0,5.4)	0.1 (0.0,0.4)
Gastroenteritis	2 (0.1%)	0	2 (<0.1%)	0	0	0
	0.1 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.2)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)
Osteomyelitis	1 (<0.1%)	0	1 (<0.1%)	2 (0.1%)	0	2 (0.1%)
	0.0 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.1 (0.0,0.4)	0.0 (0.0,5.4)	0.1 (0.0,0.4)
Pyelonephritis	1 (<0.1%)	0	1 (<0.1%)	2 (0.1%)	0	2 (0.1%)
	0.0 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.1 (0.0,0.4)	0.0 (0.0,5.4)	0.1 (0.0,0.4)

The RA Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg q.d., filgotinib 200 mg q.d. (with or without MTX or csDMARDs).
Multiple AEs were counted only once per subject for each treatment period for each PT. PTs were presented by descending order of total frequencies.
Serious infectious adverse events were defined as all PTs in the infections and infestations System Organ Class (SOC) that were SAEs.
Adverse events were coded according to MedDRA Version 22.0.
EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact poisson method was used to calculate the 95% CI (Ulm 1990).

UC: In the Induction Studies, the following incidence rates of serious infections were observed:

Table 14: EAIRs of Treatment-Emergent Serious Infections by Preferred Term, GS-US-418-3898 Induction Studies Cohort 1 (Cohorts A and B Combined; Safety Analysis Set)

	Filgotinib 200 mg (N=507)	Filgotinib 100 mg (N=562)	Placebo (N=279)	EAIR Difference (95% CI)		
Preferred Term	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
Subjects with TEAEs of Serious Infection	3/108.6	6/119.6	3/59.0			
	2.8 (0.6,8.1)	5.0 (1.8,10.9)	5.1 (1.0,14.9)	-2.3 (-12.3,4.3)	-0.1 (-10.3,7.1)	-2.3 (-8.5,3.9)
Gastroenteritis viral	1/108.8	0/120.2	1/59.2			
	0.9 (0.0,5.1)	0.0 (0.0,3.1)	1.7 (0.0,9.4)	-0.8 (-8.5,3.7)	-1.7 (-9.4,1.8)	0.9 (-2.3,5.1)
Sepsis	0/108.9	2/120.0	0/59.3			
	0.0 (0.0,3.4)	1.7 (0.2,6.0)	0.0 (0.0,6.2)	0.0 (-6.2,3.4)	1.7 (-4.7,6.0)	-1.7 (-6.0,2.0)
Anal abscess	0/108.9	1/120.1	0/59.3			
	0.0 (0.0,3.4)	0.8 (0.0,4.6)	0.0 (0.0,6.2)	0.0 (-6.2,3.4)	0.8 (-5.4,4.6)	-0.8 (-4.6,2.7)
Appendicitis	0/108.9	1/120.1	0/59.3			
	0.0 (0.0,3.4)	0.8 (0.0,4.6)	0.0 (0.0,6.2)	0.0 (-6.2,3.4)	0.8 (-5.4,4.6)	-0.8 (-4.6,2.7)
Campylobacter gastroenteritis	0/108.9	0/120.2	1/59.2			
	0.0 (0.0,3.4)	0.0 (0.0,3.1)	1.7 (0.0,9.4)	-1.7 (-9.4,2.1)	-1.7 (-9.4,1.8)	0.0 (-3.1,3.4)
Cellulitis	0/108.9	0/120.2	1/59.2			
	0.0 (0.0,3.4)	0.0 (0.0,3.1)	1.7 (0.0,9.4)	-1.7 (-9.4,2.1)	-1.7 (-9.4,1.8)	0.0 (-3.1,3.4)
Clostridium difficile infection	1/108.8	0/120.2	0/59.3			
	0.9 (0.0,5.1)	0.0 (0.0,3.1)	0.0 (0.0,6.2)	0.9 (-5.4,5.1)	0.0 (-6.2,3.1)	0.9 (-2.3,5.1)
Dengue fever	1/108.8	0/120.2	0/59.3			
	0.9 (0.0,5.1)	0.0 (0.0,3.1)	0.0 (0.0,6.2)	0.9 (-5.4,5.1)	0.0 (-6.2,3.1)	0.9 (-2.3,5.1)
Gastroenteritis	0/108.9	1/120.1	0/59.3			
	0.0 (0.0,3.4)	0.8 (0.0,4.6)	0.0 (0.0,6.2)	0.0 (-6.2,3.4)	0.8 (-5.4,4.6)	-0.8 (-4.6,2.7)
Osteomyelitis	0/108.9	0/120.2	1/59.2			
	0.0 (0.0,3.4)	0.0 (0.0,3.1)	1.7 (0.0,9.4)	-1.7 (-9.4,2.1)	-1.7 (-9.4,1.8)	0.0 (-3.1,3.4)
Staphylococcal infection	0/108.9	1/120.1	0/59.3			
	0.0 (0.0,3.4)	0.8 (0.0,4.6)	0.0 (0.0,6.2)	0.0 (-6.2,3.4)	0.8 (-5.4,4.6)	-0.8 (-4.6,2.7)

Source document: Filgotinib UC ISS, Table 2.2.6.3
EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1. TEAEs were defined as any AEs that began on or after study first dose date and up to 30 days after the last dose date within the same study or one day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each PT. PTs were presented by descending order of the total frequencies.

AEs of serious infections were defined as all serious AEs in the Infections and Infestations SOC. Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.

In the Maintenance Study, the following incidence rates of serious infections were observed:

Table 15: EAIRs of Treatment-Emergent Serious Infections by Preferred Term, Cohort 2: GS-US-418-3898 Maintenance Study (Safety Analysis Set)

	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg				Induction Placebo
	Maintenance			Maintenance			Maintenance	Maintenance
Preferred Term	Filgotinib 200 mg (N=202) n/PYE EAIR (95% CI)	Placebo (N=99) n/PYE EAIR (95% CI)	Filgotinib 200 mg vs Placebo EAIR Diff (95% CI)	Filgotinib 100 mg (N=179) n/PYE EAIR (95% CI)	Placebo (N=91) n/PYE EAIR (95% CI)	Filgotinib 100 mg vs Placebo EAIR Diff (95% CI)	Filgotinib 200 mg vs 100 mg EAIR Diff (95% CI)	Placebo (N=93) n/PYE EAIR (95% CI)
Subjects with TEAEs of Serious Infection	2/153.9	0/55.3		3/120.2	2/52.1			1/68.9
	1.3	0.0	1.3	2.5	3.8	-1.3	-1.2	1.5
	(0.2,4.7)	(0.0,6.7)	(-5.5,4.7)	(0.5,7.3)	(0.5,13.9)	(-11.6,4.5)	(-6.1,2.7)	(0.0,8.1)
Appendicitis	1/153.9	0/55.3		2/120.2	0/52.3			0/69.0
	0.6	0.0	0.6	1.7	0.0	1.7	-1.0	0.0
	(0.0,3.6)	(0.0,6.7)	(-6.0,3.6)	(0.2,6.0)	(0.0,7.1)	(-5.5,6.0)	(-5.4,2.3)	(0.0,5.3)
Acute hepatitis B	0/154.0	0/55.3		0/120.4	1/52.2			0/69.0
	0.0	0.0	0.0	0.0	1.9	-1.9	0.0	0.0
	(0.0,2.4)	(0.0,6.7)	(-6.7,2.4)	(0.0,3.1)	(0.0,10.7)	(-10.7,1.7)	(-3.1,2.4)	(0.0,5.3)
Cellulitis	0/154.0	0/55.3		1/120.3	0/52.3			0/69.0
	0.0	0.0	0.0	0.8	0.0	0.8	-0.8	0.0
	(0.0,2.4)	(0.0,6.7)	(-6.7,2.4)	(0.0,4.6)	(0.0,7.1)	(-6.3,4.6)	(-4.6,1.7)	(0.0,5.3)
Diverticulitis	1/154.0	0/55.3		0/120.4	0/52.3			0/69.0
	0.6	0.0	0.6	0.0	0.0	0.0	0.6	0.0
	(0.0,3.6)	(0.0,6.7)	(-6.0,3.6)	(0.0,3.1)	(0.0,7.1)	(-7.1,3.1)	(-2.5,3.6)	(0.0,5.3)
Gastroenteritis viral	0/154.0	0/55.3		0/120.4	1/52.2			0/69.0
	0.0	0.0	0.0	0.0	1.9	-1.9	0.0	0.0
	(0.0,2.4)	(0.0,6.7)	(-6.7,2.4)	(0.0,3.1)	(0.0,10.7)	(-10.7,1.7)	(-3.1,2.4)	(0.0,5.3)
Paronychia	0/154.0	0/55.3		1/120.3	0/52.3			0/69.0
	0.0	0.0	0.0	0.8	0.0	0.8	-0.8	0.0
	(0.0,2.4)	(0.0,6.7)	(-6.7,2.4)	(0.0,4.6)	(0.0,7.1)	(-6.3,4.6)	(-4.6,1.7)	(0.0,5.3)
Pneumonia	0/154.0	0/55.3		0/120.4	0/52.3			1/68.9
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.5
	(0.0,2.4)	(0.0,6.7)	(-6.7,2.4)	(0.0,3.1)	(0.0,7.1)	(-7.1,3.1)	(-3.1,2.4)	(0.0,8.1)

Source document: Filgotinib UC ISS, Table 2.2.6.4
EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA, Version 22.1. TEAEs were defined as any adverse events (AEs) that began on or after study first dose date and up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each PT. PTs were presented by descending order of the total frequencies. AEs of serious infections were defined as all serious AEs in the Infections and Infestations SOC. Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.

In the integrated data for UC, which includes the subjects treated in Study GS-US-418-3898 and the long-term extension Study GS-US-418-3899, the following event rates were observed:

Table 16: EAERs of Treatment-Emergent Serious Infections by Preferred Term, Cohort 3: GS-US-418-3898 and GS-US-418-3899 combined (Safety Analysis Set)

	Non-Model based descriptive statistics			Model based EAER Ratio (95% CI)		
Preferred Term	Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)	Placebo (N=469) (PYE=324.7) n (EAER*)	Filgotinib 200 mg vs. Placebo	Filgotinib 100 mg vs. Placebo	Filgotinib 200 mg vs. 100 mg
Number of TEAE of serious infections	27 (2.2)	13 (3.5)	7 (2.2)	1.0 (0.3,2.8)	2.0 (0.6,6.9)	0.5 (0.2,1.2)
Appendicitis[#$]	1 (0.1)	4 (1.1)	0	NEst	NEst	0.1 (0.0,1.2)
Cellulitis[#]	2 (0.2)	2 (0.5)	1 (0.3)	0.6 (0.1,7.1)	4.4 (0.1,168.1)	0.1 (0.0,2.0)
Pneumonia[#$]	4 (0.3)	0	1 (0.3)	1.4 (0.1,12.6)	NEst	NEst
Gastroenteritis viral	1 (0.1)	0	2 (0.6)	NEst	NEst	NEst
Anal abscess	1 (0.1)	1 (0.3)	0	NEst	NEst	NEst
Clostridium difficile infection	2 (0.2)	0	0	NEst	NEst	NEst
Diverticulitis	2 (0.2)	0	0	NEst	NEst	NEst
Infectious pleural effusion	2 (0.2)	0	0	NEst	NEst	NEst
Paronychia	0	2 (0.5)	0	NEst	NEst	NEst
Sepsis	0	2 (0.5)	0	NEst	NEst	NEst
Acute hepatitis B	0	0	1 (0.3)	NEst	NEst	NEst
Bursitis infective	1 (0.1)	0	0	NEst	NEst	NEst
Campylobacter gastroenteritis	0	0	1 (0.3)	NEst	NEst	NEst
Dengue fever	1 (0.1)	0	0	NEst	NEst	NEst
Gastroenteritis	0	1 (0.3)	0	NEst	NEst	NEst
Gastroenteritis clostridial	1 (0.1)	0	0	NEst	NEst	NEst
Herpes zoster	1 (0.1)	0	0	NEst	NEst	NEst
Lung abscess	1 (0.1)	0	0	NEst	NEst	NEst
Osteomyelitis	0	0	1 (0.3)	NEst	NEst	NEst
Peritonitis	1 (0.1)	0	0	NEst	NEst	NEst
Peritonsillar abscess	1 (0.1)	0	0	NEst	NEst	NEst
Pyelonephritis acute	1 (0.1)	0	0	NEst	NEst	NEst
Renal abscess	1 (0.1)	0	0	NEst	NEst	NEst
Septic pulmonary embolism	1 (0.1)	0	0	NEst	NEst	NEst
Staphylococcal infection	0	1 (0.3)	0	NEst	NEst	NEst
Subcutaneous abscess	1 (0.1)	0	0	NEst	NEst	NEst
Urinary tract infection	1 (0.1)	0	0	NEst	NEst	NEst

Source document: Filgotinib UC ISS, Table 2.4.2.4
EAER = exposure-adjusted event rate per 100 PYE; EAER* = (number of events/PYE)*100; NEst = not estimable. TEAE = treatment-emergent adverse event. # Data contributing to the zero event count for a period across all treatment groups were removed from the model based analysis.
$ Data contributing to the zero event count for only one treatment group were removed from the model based analysis.
AEs were coded according to MedDRA, Version 22.1. AEs of serious infections were defined as all serious AEs in the Infections and Infestations SOC. Model based EAER ratio and corresponding 95% CI were estimated using generalised estimating equations (GEE) model for longitudinal

count data including treatment group adjusted for treatment period and patient population (biologic-naïve or biologic-experienced) with an offset of natural log of exposure time.

Opportunistic infections

Table 17: RA: EAIRs of Treatment-Emergent Opportunistic Infectious Adverse Events by Preferred Term (Safety Analysis Set, As Treated Subjects)

Preferred Term	Filgotinib 200 mg q.d.			Filgotinib 100 mg q.d.		
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)
Number (%) of Subjects with Any Treatment-Emergent Infectious Adverse Event of Interest (Opportunistic Infections)	4 (0.2%)	1 (0.2%)	5 (0.2%)	4 (0.3%)	0	4 (0.2%)
Oesophageal candidiasis	2 (0.1%)	1 (0.2%)	3 (0.1%)	1 (<0.1%)	0	1 (<0.1%)
	0.1 (0.0,0.2)	0.1 (0.0,0.5)	0.1 (0.0,0.2)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)
Pneumonia cryptococcal	2 (0.1%)	0	2 (<0.1%)	0	0	0
	0.1 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.2)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)
Tuberculosis	0	0	0	1 (<0.1%)	0	1 (<0.1%)
	0.0 (0.0,0.1)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)
Herpes zoster disseminated	1 (<0.1%)	0	1 (<0.1%)	0	0	0
	0.0 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)
Lymph node tuberculosis	0	0	0	1 (<0.1%)	0	1 (<0.1%)
	0.0 (0.0,0.1)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)
Meningitis tuberculous	0	0	0	1 (<0.1%)	0	1 (<0.1%)
	0.0 (0.0,0.1)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)
Pneumocystis jirovecii pneumonia	0	0	0	0	0	0
	0.0 (0.0,0.1)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)
Pulmonary tuberculosis	0	0	0	1 (<0.1%)	0	1 (<0.1%)
	0.0 (0.0,0.1)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)

The RA Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg q.d., filgotinib 200 mg q.d. (with or without MTX or csDMARDs). PTs were presented by descending order of total frequencies.
AEs of special interest are identified by either lab results, standardised MedDRA queries, or sponsor defined MedDRA Search Terms (MSTs), or a combination of these methods.
Adverse events were coded according to MedDRA Version 22.0.
EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact poisson method was used to calculate the 95% CI (Ulm 1990).

UC: In the Induction Studies, the following incidence rates of opportunistic infections were observed:

Table 18: EAIRs of Treatment-Emergent Opportunistic Infections by Preferred Term GS-US-418-3898 Induction Studies: Cohorts A and B combined (Safety Analysis Set)

Preferred Term	Filgotinib 200 mg (N=507)	Filgotinib 100 mg (N=562)	Placebo (N=279)	EAIR Difference (95% CI)		
	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
Subjects with TEAEs of Opportunistic Infections	1/108.6	0/120.2	0/59.3			
	0.9 (0.0,5.1)	0.0 (0.0,3.1)	0.0 (0.0,6.2)	0.9 (-5.4,5.1)	0.0 (-6.2,3.1)	0.9 (-2.3,5.1)
Oesophageal candidiasis	1/108.6	0/120.2	0/59.3			
	0.9 (0.0,5.1)	0.0 (0.0,3.1)	0.0 (0.0,6.2)	0.9 (-5.4,5.1)	0.0 (-6.2,3.1)	0.9 (-2.3,5.1)

Source document: Filgotinib UC ISS, Table 2.2.8.3
EAIR = exposure-adjusted incidence rate per 100 PYE.; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. TEAEs were defined as any AEs that began on or after study first dose date and up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier.
Multiple AEs were counted only once per subject for each Preferred Term. Preferred terms were presented by descending order of the total frequencies. AEs of opportunistic infections were defined by the MST List developed by Gilead. Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.

No TEAE of opportunistic infections were reported for filgotinib-treated subjects during the Maintenance Study.

In the integrated data for UC, which includes the subjects treated in Study GS-US-418-3898 and the long-term extension Study GS-US-418-3899, the following event rates of opportunistic infections were observed:

Table 19: EAERs of Treatment-Emergent Opportunistic Infections by Preferred Term, Cohort 3: GS-US-418-3898 and GS-US-418-3899 Combined (Safety Analysis Set)

Preferred Term	Non-model based Descriptive Statistics			Model based EAER Ratio (95% CI)		
	Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)	Placebo (N=469) (PYE=324.7) n (EAER*)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
Number of Treatment-Emergent Adverse Events of Opportunistic Infections[#,$]	3 (0.2)	1 (0.3)	0	NEst	NEst	0.7 (0.1,7.3)
Cytomegalovirus infection[#,$]	1 (0.1)	1 (0.3)	0	NEst	NEst	0.2 (0.0,0.7)
Cytomegalovirus enteritis	1 (0.1)	0	0	NEst	NEst	NEst
Oesophageal candidiasis	1 (0.1)	0	0	NEst	NEst	NEst

Source document: Filgotinib UC ISS, Table 2.4.2.6
EAER = exposure-adjusted event rate per 100 PYE; EAER* = (number of events/PYE)*100; # Data contributing to the zero event count for a period across all treatment groups were removed from the model based analysis. $ Data contributing to the zero event count for only one treatment group were removed from the model based analysis. NEst = not estimable. TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. AEs of opportunistic infections were defined by the MST List developed by Gilead. Model based EAER ratio and

corresponding 95% CI were estimated using GEE model for longitudinal count data including treatment group adjusted for treatment period and patient population (biologic-naïve or biologic-experienced) with an offset of natural log of exposure time.

Risk factors and risk groups:

Patients with RA are at increased risk of developing infections, particularly septic arthritis and pulmonary infections, compared to those without RA. The reasons are multifactorial, including a poorly functioning immune system and concomitant use of immunosuppressant medications such as glucocorticoids.

Tuberculosis (TB) and other opportunistic infections (OIs) occur more frequently in patients with RA, and this risk is elevated by the use of prednisone and certain biological DMARDs (Ramiro et al. 2014).

Patients with RA who are very elderly, >75 years, on concomitant immunosuppressive therapy, or who have comorbid conditions such as diabetes, may be at increased risk of infection.

Patients with UC are at increased risk of developing OIs, including fungal, bacterial, and viral infections compared to those without UC. The immunomodulators commonly used for UC including small molecules and biologics have been associated with increased risk of OIs, and the use of more than one immunomodulator at a time may carry an increased risk of more than 14-fold. Additionally, patients with UC commonly exhibit other risk factors for OIs including malnutrition, older age, and chronic medical conditions such as diabetes (Rahier et al. 2014; Magro et al. 2017; Sheriff et al. 2020). These predisposing factors not only lower the patient's resistance to OI, but also enable the infection to develop and progress to serious infection (Rahier et al. 2014; Magro et al. 2017; Wisniewski et al. 2020).

Preventability:

Section 4.3 of the SmPC contraindicates administration of filgotinib to patients with active TB or active serious infections. Section 4.4 of the SmPC provides advice on administering filgotinib to patients with a history of, or risk factors for, serious, chronic, recurrent, or opportunistic infections. Patients should be advised to report signs and symptoms of possible infections to their healthcare provider. Healthcare professionals should carefully monitor patients who develop new infections and the treatment of infections and interruption of filgotinib therapy as appropriate should prevent an adverse outcome.

General preventative measures, for example screening for infections such as TB, and adhering to the minimal levels for neutrophils and lymphocytes recommended in the SmPC before initiating treatment, should minimise the risk of infection.

Additional risk minimisation materials (HCP guide, PAC) provide advice on the management of infections.

Impact on the risk-benefit balance of the product:

Events of serious infections and opportunistic infections have been reported during treatment of subjects with RA and subjects with UC with filgotinib. However, considering the overall burden

of the disease and the quality of life in RA and in UC, and the low incidence of serious infections and opportunistic infections seen in the RA and UC clinical trial programs, the overall benefit-risk balance for filgotinib remains positive.

Public health impact:

Low, as potential effects would be limited to the individual patient and that prescribers are accustomed to treating serious and opportunistic infections in this target population.

SVII.3.1.1.2 Herpes Zoster

Potential mechanisms:

The JAK/STAT pathway is involved in the signaling of numerous interferons, interleukins and cytokines that are involved in the immuno-inflammatory response. In addition, the underlying disease and concomitant use of immunosuppressive therapies increase the risk of herpes zoster in RA patients.

Evidence source(s) and strength of evidence:

RA: Herpes zoster has been reported with the use of other JAK inhibitors and other immunomodulatory drugs used to treat RA, such as TNF inhibitors. However, from the pivotal clinical trial data for filgotinib in the ISS, the rate of herpes zoster is lower than that published for bDMARDs, csDMARDs and JAK inhibitors (Chakravarty 2017; Dhillon 2017; Genovese et al. 2019; Wollenhaupt et al. 2019; Cohen et al. 2020). The ISS is based on a pooled dataset of Phase 2b and 3 studies in RA of subjects receiving at least 1 dose of filgotinib 100 mg or 200 mg q.d. to support the marketing authorisation application for RA.

UC: EAIRs of herpes zoster infections were low across all treatment groups in the Induction and Maintenance studies.

As patients with RA and patients with UC are at a higher risk of herpes zoster, compared to age matched controls, and the use of immunomodulatory therapy is a possible contributing factor, herpes zoster has been classified as an important identified risk warranting further study as specified in the PV plan of this RMP.

Characterisation of the risk:

Herpes zoster is an ADR for filgotinib.

RA: In the pooled data that comprises the ISS for RA, the following rates were seen for the events of herpes zoster.

Table 20: EAIR of Treatment-Emergent Herpes Zoster Adverse Events by Preferred Term Safety Analysis Set As Treated Subjects

Preferred Term	Filgotinib 200 mg q.d.			Filgotinib 100 mg q.d.		
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)
Herpes zoster	54 (3.0%)	18 (4.0%)	72 (3.2%)	23 (1.5%)	0	23 (1.4%)
	1.8 (1.4,2.3)	1.7 (1.0,2.7)	1.8 (1.4,2.2)	1.2 (0.7,1.8)	0.0 (0.0,5.4)	1.1 (0.7,1.7)
Genital herpes zoster	1 (<0.1%)	0	1 (<0.1%)	0	0	0
	0.0 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)
Herpes zoster disseminated	1 (<0.1%)	0	1 (<0.1%)	0	0	0
	0.0 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)
Ophthalmic herpes zoster	1 (<0.1%)	0	1 (<0.1%)	0	0	0
	0.0 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.0 (0.0, 0.2)	0.0 (0.0, 5.4)	0.0 (0.0,0.2)

The RA Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg q.d., filgotinib 200 mg q.d. (with or without MTX or csDMARDs). PTs were presented by descending order of total frequencies.
AEs of special interest are identified by either lab results, standardised MedDRA queries, or sponsor defined MSTs, or a combination of these methods.
Adverse events were coded according to MedDRA Version 22.0. EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact poisson method was used to calculate the 95% CI (Ulm 1990).

UC: In the Induction Studies, the following rates of herpes zoster were observed:

Table 21: EAIRs of Treatment-Emergent Herpes Zoster by Preferred Term GS-US-418-3898 Induction Studies Cohort 1 (Cohorts A and B Combined; Safety Analysis Set)

Preferred Term	Filgotinib 200 mg (N=507)	Filgotinib 100 mg (N=562)	Placebo (N=279)	EAIR Difference (95% CI)		
	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
Subjects with TEAEs of Herpes Zoster	3/108.4	1/120.1	0/59.3			
	2.8 (0.6,8.1)	0.8 (0.0,4.6)	0.0 (0.0,6.2)	2.8 (-3.8,8.1)	0.8 (-5.4,4.6)	1.9 (-2.5,7.3)
Herpes zoster	3/108.4	1/120.1	0/59.3			
	2.8 (0.6,8.1)	0.8 (0.0,4.6)	0.0 (0.0,6.2)	2.8 (-3.8,8.1)	0.8 (-5.4,4.6)	1.9 (-2.5,7.3)

Source document: Filgotinib UC ISS, Table 2.2.7.3
EAIR = exposure-adjusted incidence rate per 100 PYE. PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. TEAEs were defined as any AEs that began on or after study first dose date and up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each Preferred Term. AEs of herpes zoster were defined by the MST List developed by Gilead. Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs

In the Maintenance Study, the following incidence rates of herpes zoster were observed:

Table 22: EAIRs of Treatment-Emergent Herpes Zoster by Preferred Term Cohort 2: GS-US-418-3898 Maintenance Study (Safety Analysis Set)

	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg				Induction Placebo
	Maintenance			Maintenance			Maintenance	Maintenance
Preferred Term	Filgotinib 200 mg (N=202) n/PYE EAIR (95% CI)	Placebo (N=99) n/PYE EAIR (95% CI)	Filgotinib 200 mg vs Placebo EAIR Diff (95% CI)	Filgotinib 100 mg (N=179) n/PYE EAIR (95% CI)	Placebo (N=91) n/PYE EAIR (95% CI)	Filgotinib 100 mg vs Placebo EAIR Diff (95% CI)	Filgotinib 200 mg vs 100 mg EAIR Diff (95% CI)	Placebo (N=93) n/PYE EAIR (95% CI)
Subjects with TEAEs of Herpes Zoster	1/153.9	0/55.3		0/120.4	1/51.6			0/69.0
	0.6	0.0	0.6	0.0	1.9	-1.9	0.6	0.0
	(0.0,3.6)	(0.0,6.7)	(-6.0,3.6)	(0.0,3.1)	(0.0,10.8)	(-10.8,1.7)	(-2.5,3.6)	(0.0,5.3)
Herpes zoster	1/153.9	0/55.3		0/120.4	1/51.6			0/69.0
	0.6	0.0	0.6	0.0	1.9	-1.9	0.6	0.0
	(0.0,3.6)	(0.0,6.7)	(-6.0,3.6)	(0.0,3.1)	(0.0,10.8)	(-10.8,1.7)	(-2.5,3.6)	(0.0,5.3)

Source document: Filgotinib UC ISS, Table 2.2.7.4
EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. TEAEs were defined as any adverse events (AEs) that began on or after study first dose date and up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each PT. PTs were presented by descending order of the total frequencies. AEs of herpes zoster were defined by the MST List developed by Gilead. Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs

In the integrated data for UC, which includes the subjects treated in Study GS-US-418-3898 and the long-term extension Study GS-US-418-3899, the following event rates of herpes zoster were observed:

Table 23: EAERs of Treatment-Emergent Herpes Zoster by Preferred Term, Cohort 3: GS-US-418-3898 and GS-US-418-3899 Combined (Safety Analysis Set)

	Non-model based Descriptive Statistics			Model based EAER Ratio (95% CI)		
Preferred Term	Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)	Placebo (N=469) (PYE=324.7) n (EAER*)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
Number of Treatment-Emergent Adverse Events of Herpes Zoster	22 (1.8)	1 (0.3)	1 (0.3)	5.3 (0.7,37.7)	0.8 (0.1,12.5)	6.2 (0.8,47.4)
Herpes zoster	22 (1.8)	1 (0.3)	1 (0.3)	5.3 (0.7,37.7)	0.8 (0.1,12.5)	6.2 (0.8,47.4)

Source document: Filgotinib UC ISS, Table 2.4.2.5
EAER = exposure-adjusted event rate per 100 PYE; EAER* = (number of events /PYE)*100;
NEst = not estimable; TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. AEs of herpes zoster were defined by the MST List developed by Gilead.
Model based EAER ratio and corresponding 95% CI were estimated using GEE model for longitudinal count data including treatment group adjusted for treatment period and patient population (biologic-naïve or biologic-experienced) with an offset of natural log of exposure time.

Risk factors and risk groups:

RA: Patients with RA are at increased risk of developing herpes zoster compared with age-matched healthy adults (Chakravarty 2017). The reasons are multifactorial, including a

poorly functioning immune system and concomitant use of immunosuppressant medications such as glucocorticoids, increased age and female sex (Chakravarty 2017; Kawai and Yawn 2017; Ramiro et al. 2017).

UC: The incidence of zoster is higher in patients with UC compared with their matched controls in the general population (Gupta et al. 2006). An increased risk of zoster in patients with IBD is hypothesised based on altered immune function, particularly among patients receiving immunosuppressant medications. The increased risk observed among IBD patients compared with their matched controls is likely multifactorial. Patients with active IBD have dysregulation of the immune system that could increase the risk of zoster. However, the use of immuno-suppressant medications is likely as important, or more important. Use of thiopurines, anti-TNF agents, combination therapy, and corticosteroids in UC patients increases HZ risk (Long et al. 2013).

Preventability:

Preventative measures, which prescribers can consider, are testing for herpes zoster infection and utilisation of prophylactic zoster vaccination, in accordance with local vaccination guidelines. Monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during treatment with filgotinib. Treatment with filgotinib should be interrupted for patients who develop herpes zoster (as outlined in Section 4.4 of the SmPC).

Additional risk minimisation materials (HCP guide, PAC) provide advice on the management of herpes zoster.

Impact on the risk-benefit balance of the product:

Cases of herpes zoster have been reported during treatment with filgotinib. However, considering the overall burden of the disease and the quality of life for patients with RA and patients with UC, and the low incidence of herpes zoster seen in the RA and UC clinical trial programs, the overall benefit-risk balance for filgotinib remains positive.

Public health impact:

Low, as potential effects would be limited to the individual patient and prescribers are accustomed to managing herpes zoster with vaccination and widely available antivirals in this target population.

SVII.3.1.2 Important Potential Risks

SVII.3.1.2.1 Embryolethality and Teratogenicity

Potential mechanisms:

The mechanism of embryolethality and teratogenicity for filgotinib is unknown.

Evidence source(s) and strength of evidence:

Non-clinical findings of embryolethality and teratogenicity were observed at exposures equivalent to the human dose of 200 mg q.d.

Embryo-fetal development studies were conducted in rats and rabbits. Visceral and skeletal malformations and/or variations were observed at all dose levels of filgotinib and its active metabolite.

Characterisation of the risk:

The relevance of the non-clinical findings to human use is unknown.

Cumulatively to 31 March 2020, there were 23 first trimester exposures in filgotinib-treated subjects in the filgotinib development program in RA and UC indications: 19 pregnancies in subjects with RA and 4 pregnancies in subjects with UC.

The outcomes of the pregnancies were: 7 spontaneous abortions, 3 elective abortions, 2 ectopic pregnancies, and 9 live births. Additionally, pregnancy outcomes are pending for 2 cases. Of the 9 live births, 1 case, in a subject with RA, reported a congenital abnormality (Pentalogy of Fallot). There were 8 additional pregnancies in clinical study subjects with other indications, of which, 4 received filgotinib and 4 received blinded study drug. The outcomes were: 2 live births, 2 elective abortions, 1 spontaneous abortion, and for 3 pregnancies the outcome is pending.

Risk factors and risk groups:

Pregnant women and women of childbearing potential.

Preventability:

Filgotinib is contraindicated in pregnancy (SmPC Section 4.3).

Section 4.6 of the SmPC provides advice on contraception to women of childbearing potential.

Additional risk minimisation materials (HCP guide, PAC) provide advice on avoidance of use in pregnancy.

Impact on the risk-benefit balance of the product:

RA is approximately 2 to 3 times more common in women than in men. The female RA population is mostly older than childbearing age, with peak age of onset between 40 to 60 years and highest prevalence at age 70 years and over. Younger women have the option of interrupting, minimising or switching treatment for a pregnancy. Common comedications, including MTX, carry the same risk; consequently, Prescribers are experienced in managing this risk for their female RA patients. The risk minimisation measures in place mitigate this risk. Therefore, the benefit-risk balance remains positive.

Public health impact:

Given the warning for embryolethality and teratogenicity to women of childbearing potential and guidance to use effective contraception while being treated with filgotinib in the SmPC and package leaflet (PL) and included in the HCP guide and PAC, the potential public health impact would be low. Additionally, in patients with RA, the majority of female patients are not of childbearing potential due to advanced age (Arthritis 2019), which further lowers the potential public health impact in this population.

SVII.3.1.2.2 Malignancy

Potential mechanisms:

The potential role of JAK inhibition in malignancy remains unknown. Non-clinical studies did not indicate that filgotinib is carcinogenic.

Evidence source(s) and strength of evidence:

Malignancy is considered a class effect of JAK inhibitors.

RA: Patients with RA have an increased risk of some types of malignancy, for example lung, lymphoma, as well as overall malignancy (Simon et al. 2015). It is currently unknown if filgotinib affects this risk, or if filgotinib will increase the risk of recurrence of malignancy, or of a secondary malignancy, in this patient population. The incidence rate for overall malignancies in filgotinib-treated groups for the ISS dataset was lower than published rates in the RA population (Simon et al. 2015).

UC: Several population-based studies have shown that patients with UC are at increased risk of developing intestinal and extraintestinal malignancies compared to those without UC (Kappelman et al. 2014; Wang et al. 2016; Hovde et al. 2017; Loo et al. 2019). It is not known if filgotinib affects this risk, or if filgotinib will increase the risk of recurrence of malignancy, or of a secondary malignancy, in this patient population. The EAIRs of malignancies were low among filgotinib-treated subjects in the Induction and Maintenance studies.

However, clinical trial data are insufficient to assess the potential incidence of malignancies.

With patients with RA and patients with UC being at a higher risk of certain malignancies, and the long-term effects of immunomodulatory therapy on this risk uncertain, malignancy has been classified as an important potential risk warranting further study as specified in the PV plan of this RMP.

Characterisation of the risk:

RA: Exposure-based analysis of the pooled data comprising the ISS for RA did not identify any signals for malignancy. The ISS is a pooled dataset of Phase 2b and 3 studies in RA of subjects receiving at least 1 dose of filgotinib 100 mg or 200 mg q.d. to support the marketing authorisation application for RA.

In the pooled data that comprise the ISS for RA, the following incidence rates were seen for the most frequently occurring malignancies (excluding non-melanoma skin cancer).

Table 24: EAIRs of TEAEs of Interest (Malignancy excluding NMSC) Occurring in ≥2 Subjects by Preferred Term (Safety Analysis Set, As Treated Subjects)

Preferred Term	Filgotinib 200 mg q.d.			Filgotinib 100 mg q.d.		
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)
Number (%) of Subjects with Any Treatment-Emergent Adverse Event of Interest (Malignancy Excluding Non-melanoma Skin Cancer)	18 (1.0%)	4 (0.9%)	22 (1.0%)	11 (0.7%)	0	11 (0.7%)
Prostate cancer	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
	0.0 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)
Breast cancer	1 (<0.1%)	0	1 (<0.1%)	0	0	0
	0.0 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.1)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)
Intraductal proliferative breast lesion	2 (0.1%)	0	2 (<0.1%)	0	0	0
	0.1 (0.0,0.2)	0.0 (0.0,0.4)	0.0 (0.0,0.2)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)
Non-Hodgkin's lymphoma	0	2 (0.4%)	2 (<0.1%)	0	0	0
	0.0 (0.0,0.1)	0.2 (0.0,0.7)	0.0 (0.0,0.2)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)

The RA Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg q.d., filgotinib 200 mg q.d. (with or without MTX or csDMARDs).
Multiple AEs were counted only once per subject for each treatment period for each PT. PTs were presented by descending order of total frequencies.
AEs of special interest are identified by either lab results, standardised MedDRA queries, or sponsor defined MSTs, or a combination of these methods.
Adverse events were coded according to MedDRA Version 22.0.
EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact poisson method was used to calculate the 95% CI (Ulm 1990).

UC: In the Induction Studies, the following incidence rates of Malignancy excluding NMSC were observed:

Table 25: EAIRs of TEAEs of Malignancies Excluding NMSC by Preferred Term, GS-US-418-3898 Induction Studies Cohort 1 (Cohorts A and B Combined; Safety Analysis Set)

Preferred Term	Filgotinib 200 mg (N=507) n/PYE EAIR (95% CI)	Filgotinib 100 mg (N=562) n/PYE EAIR (95% CI)	Placebo (N=279) n/PYE EAIR (95% CI)	EAIR Difference (95% CI) Filgotinib 200 mg vs. Placebo	Filgotinib 100 mg vs. Placebo	Filgotinib 200 mg vs. 100 mg
Subjects with TEAEs of Malignancy excluding NMSC	1/108.7 0.9 (0.0,5.1)	1/120.2 0.8 (0,0,4.6)	0/59.3 0.0 (0.0,6.2)	0.9 (-5.4,5.1)	0.8 (-5.4,4.6)	0.1 (-3.8,4.4)
Breast cancer	1/108.7 0.9 (0.0,5.1)	0/120.2 0.0 (0.0,3.1)	0/59.3 0.0 (0.0,6.2)	0.9 (-5.4,5.1)	0.0 (-6.2,3.1)	0.9 (-2.3,5.1)
Colon cancer	0/108.9 0.0 (0.0,3.4)	1/120.2 0.8 (0,0,4.6)	0/59.3 0.0 (0.0,6.2)	0.0 (-6.2,3.4)	0.8 (-5.4,4.6)	-0.8 (-4.6,2.7)

Source document: Filgotinib UC ISS, Table 2.2.9.3
EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. TEAEs were defined as any adverse events (AEs) that began on or after study first dose date and up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each PT. PTs were presented by descending order of the total frequencies. AEs of malignancy excluding NMSC were defined by the MST list developed by Gilead.
Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.

In the Maintenance Study, the following incidence rates of Malignancy excluding NMSC were observed:

Table 26: EAIRs of TEAEs of Malignancies Excluding NMSC by Preferred Term, Cohort 2: GS-US-418-3898 Maintenance Study (Safety Analysis Set)

	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg				Induction Placebo
	Maintenance			Maintenance			Maintenance	Maintenance
Preferred Term	Filgotinib 200mg (N=202) n/PYE EAIR (95% CI)	Placebo (N=99) n/PYE EAIR (95% CI)	Filgotinib 200mg vs. Placebo EAIR Difference (95% CI)	Filgotinib 100mg (N=179) n/PYE EAIR (95% CI)	Placebo (N=91) n/PYE EAIR (95% CI)	Filgotinib 100mg vs. Placebo EAIR Difference (95% CI)	Filgotinib 200mg vs. 100mg EAIR Difference (95% CI)	Placebo (N=93) n/PYE EAIR (95% CI)
Subjects with TEAEs of Malignancy excluding NMSC	1/153.9 0.6 (0.0, 3.6)	0/55.3 0.0 (0.0, 6.7)	0.6 (-6.0,3.6)	1/120.3 0.8 (0.0, 4.6)	0/52.3 0.0 (0.0, 7.1)	0.8 (-6.3,4.6)	-0.2 (-4.0,2.9)	0/69.0 0.0 (0.0,5.3)
Colon cancer	0/154.0 0.0 (0.0, 2.4)	0/55.3 0.0 (0.0, 6.7)	0.0 (-6.7,2.4)	1/120.3 0.8 (0.0, 4.6)	0/52.3 0.0 (0.0, 7.1)	0.8 (-6.3,4.6)	-0.8 (-4.6,1.7)	0/69.0 0.0 (0.0,5.3)

Preferred Term	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg				Induction Placebo
	Maintenance			Maintenance			Maintenance	Maintenance
	Filgotinib 200mg (N=202) n/PYE EAIR (95% CI)	Placebo (N=99) n/PYE EAIR (95% CI)	Filgotinib 200mg vs. Placebo EAIR Difference (95% CI)	Filgotinib 100mg (N=179) n/PYE EAIR (95% CI)	Placebo (N=91) n/PYE EAIR (95% CI)	Filgotinib 100mg vs. Placebo EAIR Difference (95% CI)	Filgotinib 200mg vs. 100mg EAIR Difference (95% CI)	Placebo (N=93) n/PYE EAIR (95% CI)
Malignant melanoma	1/153.9 0.6 (0.0, 3.6)	0/55.3 0.0 (0.0, 6.7)	0.6 (-6.0,3.6)	0/120.4 0.0 (0.0, 3.1)	0/52.3 0.0 (0.0, 7.1)	0.0 (-7.1,3.1)	0.6 (-2.5,3.6)	0/69.0 0.0 (0.0,5.3)

Source document: Filgotinib UC ISS, Table 2.2.9.4
EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. Adverse events were coded according to MedDRA Version 22.1. TEAEs were defined as any adverse events (AEs) that began on or after study first dose date and up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each PT. PTs were presented by descending order of the total frequencies. AEs of malignancy excluding NMSC were defined by the MST list developed by Gilead. Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.

In the integrated data for UC, which includes the subjects treated in Study GS-US-418-3898 and the long-term extension study GS-US-418-3899, the following event rates were observed:

Table 27: EAERs of TEAEs of Malignancies Excluding Non-melanoma Skin Cancers by Preferred Term, Cohort 3: GS-US-418-3898 and GS-US-418-3899 Combined (Safety Analysis Set)

Preferred Term	Non-model-based Descriptive Statistics			Model- based EAER Ratio (95% CI)		
	Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)	Placebo (N=469) (PYE=324.7) n (EAER*)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
Number of Treatment-Emergent Adverse Events of Malignancies Excluding Non-melanoma Skin Cancers [$]	10 (0.8)	5 (1.3)	0	NEst	NEst	0.7 (0.2,3.0)
Colon cancer [#,$]	1 (0.1)	2 (0.5)	0	NEst	NEst	0.1 (0.0,0.5)
Adenocarcinoma of colon	2 (0.2)	0	0	NEst	NEst	NEst
Breast cancer	1 (0.1)	0	0	NEst	NEst	NEst
Clear cell renal cell carcinoma	1 (0.1)	0	0	NEst	NEst	NEst
Malignant melanoma	1 (0.1)	0	0	NEst	NEst	NEst
Metastatic carcinoid tumour	1 (0.1)	0	0	NEst	NEst	NEst
Oesophageal adenocarcinoma	1 (0.1)	0	0	NEst	NEst	NEst
Papillary renal cell carcinoma	0	1 (0.3)	0	NEst	NEst	NEst
Plasma cell myeloma	0	1 (0.3)	0	NEst	NEst	NEst
Prostate cancer	1 (0.1)	0	0	NEst	NEst	NEst
Renal cell carcinoma	0	1 (0.3)	0	NEst	NEst	NEst
Uterine leiomyosarcoma	1 (0.1)	0	0	NEst	NEst	NEst

Source document: Filgotinib UC ISS, Table 2.4.2.7

EAER = exposure-adjusted event rate per 100 PYE; EAER* = (number of events/PYE)*100; # Data contributing to the zero event count for a period across all treatment groups were removed from the model based analysis. $ Data contributing to the zero event count for only 1 treatment group were removed from the model based analysis.
NEst = not estimable. TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. AEs of malignancy excluding NMSC were defined by the MST list developed by Gilead. Model based EAER ratio and corresponding 95% CI were estimated using GEE model for longitudinal count data including treatment group adjusted for treatment period and patient population (biologic-naïve or biologic-experienced) with an offset of natural log of exposure time.
Of note: clinical trial data are insufficient to assess the incidence of malignancies and long-term safety evaluations of the Phase 2b and 3 clinical trial populations are ongoing.

Risk factors and risk groups:

Patients with familial history of malignancy or lifestyle risk factors, such as tobacco or alcohol use, obesity. The risk of malignancy increases with age.

Preventability:

Early detection of malignancy and appropriate treatment can mitigate seriousness and improve outcomes.

Section 4.2 of the SmPC recommends a dose adjustment in adults at increased risk for malignancy. Section 4.4 of the SmPC provides advice on administering filgotinib to patients with a history of, or risk factors for malignancy. Additional risk minimisation materials (HCP guide, PAC) provide advice on the management of malignancies.

Impact on the risk-benefit balance of the product:

The low rates of malignancy observed in the filgotinib RA and UC clinical trial programs are not considered to impact the overall benefit-risk balance of the product. Considering the overall burden of the disease, the benefit-risk balance for filgotinib remains positive.

Public health impact:

The impact of the morbidity and mortality associated with malignancy can be high. However, at the rates observed in the filgotinib clinical trial program, the public health impact is considered to be low.

SVII.3.1.2.3 Venous Thromboembolism (Deep Venous Thrombosis and Pulmonary Embolism)

Potential mechanisms:

The potential role of JAK inhibition in developing VTE remains unknown. Non-clinical studies did not indicate that filgotinib is thrombogenic. No increases in platelet count have been observed with filgotinib treatment in patients with RA.

Evidence source(s) and strength of evidence:

VTE is considered a class effect of JAK inhibitors.

RA: VTE (deep venous thrombosis and pulmonary embolism) events positively adjudicated have been reported with filgotinib treatment in patients with RA. However, from the pooled clinical trial data for filgotinib in the indication of RA, no imbalance in reports of VTE events was noted across filgotinib (including 100 mg and 200 mg doses) and placebo or comparators, and all patients who developed a VTE event had recognised risk factors such as advanced age, immobilisation, obesity, cancer, smoking, prior history of deep venous thrombosis (DVT) and pulmonary embolism (PE), heart failure or hormone replacement therapy.

Population-based cohort studies suggested an increased risk of VTE in RA patients (Holmqvist et al. 2012; Ogdie et al. 2018). An exposure-adjusted incidence rate (EAIR) of VTE of 0.61 per 100 person-years in RA patients, which was approximately 2.4 times (95% CI 2.1-2.8) higher than the rate in the non-RA population matched for age, sex and index date, was reported in a retrospective US cohort study (Kim et al. 2013). A recent epidemiologic analysis based on a US medical claims database (Pharmetrics Plus 2019 B2, which contains adjudicated pharmacy, hospital, and medical claims sourced from commercial payers covering more than 100 million people) indicated an unadjusted VTE IR of 0.59 per PYE (95% CI 0.58-0.60).

The exposure-adjusted IR (0.2 per 100 PYE, 95% CI 0.1-0.4 and 0.0 per 100 PYE, 95% CI 0.0-0.3 for 200 mg q.d. and 100 mg q.d. respectively) of VTE events for filgotinib treatment in the pooled data is within the expected background rate of the target population based on the above literature (0.61 per 100 PYE) (Kim et al. 2013) and the real-world (claims) data (0.59 per 100 PYE).

UC: IBD including UC is a known risk factor for VTE, including DVT and PE. Patients with UC have higher risk of developing VTE compared to general population. The risk of VTE rises with increasing inflammatory burden and is highest among patients with UC hospitalised for acute disease flares (Grainge et al. 2010; Kappelman et al. 2011; Tan et al. 2013; Scoville et al. 2014; Murthy et al. 2020).

Only 1 filgotinib-treated subject reported a TEAE of PE during the UC program, and no TEAE of venous thrombosis (excluding PE) were reported by filgotinib-treated subjects in the UC program.

With RA patients and patients with UC having a higher risk of VTEs, and VTEs having been associated with some JAK inhibitors, venous thromboembolism (DVT/PE) has been classified as an important potential risk warranting further study as specified in the PV Plan of this RMP.

Characterisation of the risk:

In the pooled data that comprises pivotal clinical trial dataset of Phase 2b and 3 studies in RA subjects receiving at least 1 dose of filgotinib 100 mg or 200 mg q.d., the following rates were seen for positively adjudicated VTE (DVT/PE) events.

Table 28: EAIRs of TEAEs of Interest (VTE) by Preferred Term (Safety Analysis Set, As Treated Subjects)

Venous Thromboembolism (VTE)	Filgotinib 200 mg q.d.			Filgotinib 100 mg q.d.		
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)
Venous Thromboembolism (VTE): DVT/PE	8 (0.4%)	0	8 (0.4%)	1 (<0.1%)	0	1 (<0.1%)
	0.3 (0.1,0.5)	0.0 (0.0,0.4)	0.2 (0.1,0.4)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)
Deep Vein Thrombosis (DVT)	6 (0.3%)	0	6 (0.3%)	0	0	0
	0.2 (0.1,0.4)	0.0 (0.0,0.4)	0.1 (0.1,0.3)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)
Pulmonary Embolism (PE)	6 (0.3%)	0	6 (0.3%)	1 (<0.1%)	0	1 (<0.1%)
	0.2 (0.1,0.4)	0.0 (0.0,0.4)	0.1 (0.1,0.3)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)

The RA Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg q.d., filgotinib 200 mg q.d.(with or without MTX or csDMARDs).
Multiple AEs were counted only once per subject for each treatment period for each PT. PTs were presented by descending order of total frequencies.
AEs of special interest are identified by either lab results, standardised MedDRA queries, or sponsor defined MSTs, or a combination of these methods.
Adverse events were coded according to MedDRA Version 22.0.
EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact poisson method was used to calculate the 95% CI (Ulm 1990).

UC: In the Induction Studies, the following incidence rates were observed:

No subject reported any TEAEs of venous thrombosis (excluding PE) during the Induction Studies (Source: UC ISS Table 2.2.12.3).

Table 29: EAIRs of TEAEs of Pulmonary Embolism, GS-US-418-3898 Induction Studies Cohort 1 (Cohorts A and B Combined; Safety Analysis Set) Preferred Term

	Filgotinib 200 mg	Filgotinib 100 mg	Placebo	EAIR Difference (95% CI)		
	(N=507) n/PYE EAIR (95% CI)	(N=562) n/PYE EAIR (95% CI)	(N=279) n/PYE EAIR (95% CI)	Filgotinib 200 mg vs. Placebo	Filgotinib 100 mg vs. Placebo	Filgotinib 200 mg vs. 100 mg
Subjects with TEAEs of Pulmonary Embolism	1/108.8	0/120.2	0/59.3			
	0.9 (0.0,5.1)	0.0 (0.0,3.1)	0.0 (0.0,6.2)	0.9 (-5.4,5.1)	0.0 (-6.2,3.1)	0.9 (-2.3,5.1)
Pulmonary Embolism	1/108.8	0/120.2	0/59.3	0.9	0.0	0.9
	0.9 (0.0, 5.1)	0.0 (0.0,3.1)	0.0 (0.0,6.2)	(-5.4, 5.1)	(-6.2, 3.1)	(-2.3, 5.1)

Source document: Filgotinib UC ISS, Table 2.2.12.3, Table 2.2.13.3
EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. TEAEs were defined as any adverse events (AEs) that began on or after study first dose date and up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each PT. PTs were presented by descending order of the total frequencies. AEs of PE and AEs of venous thrombosis were defined by respective MedDRA Search Term (MST) Lists developed by Gilead.
Exact Poisson distribution method was applied to compute the 95% confidence interval (CI) of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.
No TEAE of venous thrombosis or PE were reported for filgotinib-treated subjects during the Maintenance Study.
(Source documents: ISS Table 2.2.12.4, Table 2.2.13.4)

In the integrated data for UC, which includes the subjects treated in Study GS-US-418-3898 and the long-term extension Study GS-US-418-3899, the following event rates were observed:

Table 30: EAERs of TEAEs of Venous Thrombosis and Pulmonary Embolism Cohort 3: GS-US-418-3898 and GS-US-418-3899 Combined (Safety Analysis Set)

	Non-model-based Descriptive Statistics			Model- based EAER Ratio (95% CI)		
Preferred Term	Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)	Placebo (N=469) (PYE=324.7) n (EAER*)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
Venous Thrombosis	0	0	3 (0.9)	NEst	NEst	NEst
Pulmonary Embolism	1 (0.1)	0	0	NEst	NEst	NEst

Source document: Filgotinib UC ISS, Table 2.4.2.10, Table 2.4.2.11
EAER = exposure-adjusted event rate per 100 PYE; EAER* = (number of events /PYE)*100; NEst = not estimable; TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. AEs of PE and AEs of venous thrombosis were defined by respective MST Lists developed by Gilead. Model based EAER ratio and corresponding 95% CI were estimated using GEE model for longitudinal count data including treatment group adjusted for treatment period and patient population (biologic-naïve or biologic-experienced) with an offset of natural log of exposure time.

Risk factors and risk groups:

The patients who developed VTE events with filgotinib treatment had at least one of the following recognised risk factors including prior history of VTE, advanced age, hormone replacement treatment, obesity, smoking, cancer, or immobilisation.

Preventability:

Section 4.2 of the SmPC recommends a dose adjustment in adults at increased risk for VTE. Section 4.4 of the SmPC indicates that VTE (DVT and PE) events have been reported in patients receiving JAK inhibitors including filgotinib and provides advice on administering filgotinib to patients with risk factors for VTE. In case of the occurrence of VTE events, advice is provided including temporary discontinuation of filgotinib treatment, prompt evaluation and appropriate treatment.

Additional risk minimisation materials (HCP guide, PAC) provide advice on the management of VTEs.

Impact on the risk-benefit balance of the product:

Considering that the incidence rate of VTE (DVT/PE) events in the filgotinib RA and UC clinical trial programs is low and within the expected background rate for the target population, the overall benefit-risk balance for filgotinib remains positive in view of overall burden of the disease.

Public health impact:

Although most VTE events would require hospitalisation, at a low incidence such as that observed in the filgotinib clinical trial program, the potential public health impact would be small.

SVII.3.1.2.4 Gastrointestinal Perforation

Potential mechanisms:

The mechanisms by which biologics may lead to GI perforations include impairment of host defenses either through impaired wound healing or altered immune balance in the intestine. As biologics that inhibit the IL-6 cytokine receptor (e.g. tocilizumab) have been associated with a higher risk of GI perforation compared to other therapies, a potential mechanism for JAK inhibitors is via downstream effects on IL-6 signaling (Xie et al. 2016).

Evidence source(s) and strength of evidence:

GI perforation has been reported with the use of tofacitinib in addition to other immunomodulatory drugs used in the treatment of RA and UC including TNF inhibitors. Although there is a pharmacologically plausible basis for an association between JAK inhibitors and GI perforation, there is insufficient evidence to establish it as an adverse effect of filgotinib treatment at this time. Furthermore, in UC the exposure-adjusted IR (0.1 per 100 PYE, 95% CI 0.0-0.4 and 0.0 per 100 PYE, 95% CI 0.0-0.2 for 200 mg q.d. and 100 mg q.d., respectively) for GI perforation for filgotinib treatment in the pooled data is within the expected background rate of the target population based on real-world (claims) data (0.10, 95% CI 0.10-0.11, per 100 PYE).

Patients with RA may be at an increased risk of GI perforation due to prescribed medications (NSAIDs), and/or because of the consequences of the disease process (e.g. vasculitis).

Patients with UC are at an increased risk for GI perforation compared to age matched control group (Incidence ratio of 6.05, 95% CI 5.60-6.53). However, in the UC clinical program with filgotinib, no filgotinib-treated subjects reported any treatment-emergent adverse events (TEAEs) of GI perforations.

With RA and UC patients having a higher risk of GI perforations, and GI perforations having been associated with some JAK inhibitors, GI perforations has been classified as an important potential risk warranting further study as specified in the PV plan of this RMP.

Characterisation of the risk:

RA: Exposure-based analysis of the pooled data comprising the RA ISS did not identify any signals for GI perforations. The ISS is a pooled dataset of Phase 2b and 3 studies in RA subjects receiving at least 1 dose of filgotinib 100 mg or 200 mg q.d. to support the marketing authorisation application for RA.

In the pooled data that comprises the ISS for RA, the following incidence rates were seen for GI perforations.

Table 31: EAIRs of TEAEs of Interest (GI Perforations) by Preferred Term (Safety Analysis Set, As Treated Subjects)

Treatment-Emergent Adverse Event of Interest	Filgotinib 200 mg q.d.			Filgotinib 100 mg q.d.		
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)
Gastrointestinal Perforations	3 (0.2%)	0	3 (0.1%)	0	0	0
	0.1 (0.0,0.3)	0.0 (0.0,0.4)	0.1 (0.0,0.2)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)

The RA Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg q.d., filgotinib 200 mg q.d. (with or without MTX or csDMARDs). Only the adjudicated positive MACE were included.
AEs of special interest are identified by either lab results, standardised MedDRA queries, or sponsor defined MSTs, or a combination of these methods.
Adverse events were coded according to MedDRA Version 22.0.
EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact poisson method was used to calculate the 95% CI (Ulm 1990).

UC: In the UC clinical program, no TEAE of GI perforation was reported for filgotinib-treated subjects.

Risk factors and risk groups:

Antecedent diverticulitis, use of glucocorticoids, exposure to NSAIDS, increasing age, and other GI conditions represent risk factors for GI perforation (Jagpal and Curtis 2018). Advanced age and use of immunosuppressive medications are common in the moderately to severely active RA population, therefore placing this population at greater risk.

Preventability:

No data are available to identify specific measure that can be used to prevent the occurrence of GI perforation.

Impact on the risk-benefit balance of the product:

Although GI perforation can be fatal, the benefit-risk balance of the product remains positive, given the low rate of GI perforation observed in the filgotinib RA clinical trial program.

Public health impact:

GI perforations can be costly and depending on their severity and location are potentially life-threatening events that warrant prompt medical/surgical intervention. Free perforations (that lead to leakage of bowel contents into the intra-abdominal cavity resulting in peritonitis) are associated with a high mortality rate of up to approximately 30%. However, at a low rate such as that observed in the filgotinib clinical trial program, the public health impact would be low.

SVII.3.1.2.5 Non-Melanoma Skin Cancer

Potential mechanisms:

Filgotinib is an immunomodulator that may have an impact on cancer-related immune surveillance. However, the potential role of JAK inhibition in malignancy including NMSC remains unknown.

Evidence source(s) and strength of evidence:

NMSC is considered a class effect of JAK inhibitors.

RA: NMSC has been reported with filgotinib treatment in patients with RA. From the pooled clinical trial data for filgotinib in the indication of RA, similar incidence of NMSC was noted across filgotinib (including 100 mg and 200 mg doses) and placebo or comparators. Most NMSC events were reported in white elderly (≥65 years old) patients with concomitant medication of MTX. Prior history of NMSC was noted in some patients who developed NMSC during the filgotinib treatment.

Epidemiologic studies showed an increased risk of development of NMSC in RA patients (Mellemkjaer et al. 1996; Asten et al. 1999; Chakravarty et al. 2005; Scott et al. 2016), which is in alignment with the result of a meta-analysis showing a RR of 2.02 (95% CI 1.11-3.95) for NMSC in RA patients (Askling et al. 2011). Development of NMSC in RA patients was associated with use of prednisone (RR 1.28, p=0.014) alone or with combination MTX and TNF inhibitors (RR 1.97, p=0.001), in addition to established risk factors (Chakravarty et al. 2005). A meta-analysis has recently supported the association of increased risk of skin cancers, especially squamous cell cancer (SCC) (RR 1.28, 95% CI 1.19-1.3; RR 1.30, 95% CI 1.09-1.54 respectively) in RA patients with the use of TNF inhibitors compared to RA patients without anti-TNF drugs (Wang et al. 2020).

The exposure-adjusted IR (0.2 per 100 PYE, 95% CI 0.1-0.4 and 0.1 per 100 PYE, 95% CI 0.0-0.4 for filgotinib 200 mg q.d. and 100 mg q.d., respectively) of NMSC for filgotinib treatment in the pooled data was lower than that in a real-world (claims) data (1.07 per 100 PYE, 95% CI: 1.05-1.09) in the target population of RA patients.

UC: NMSC have been reported with filgotinib treatment in patients with UC. All NMSC events were reported in Caucasian subjects, most were elderly (≥65 years old). Prior history of NMSC, and additional risk factors were noted in some patients who reported NMSC during filgotinib treatment. The incidence of NMSC is increased in patients with UC compared to general population. The increased risk for NMSC in UC population might be attributed to the underlying immune dysfunction of UC as well as the use of immunosuppressive medication, in particular thiopurine (Long et al. 2011, 2012; Kappelman et al. 2014; Loo et al. 2019).

In the Induction Studies, the EAIRs for NMSC were low: 2 subjects in the filgotinib 200 mg group experienced NMSC (1 subject experience basal cell carcinoma and 1 Bowen's disease) (EAIR = 1.8/100 PYE [95% CI: 0.2, 6.7]), 1 subject in the placebo group experienced basal cell carcinoma (EAIR = 1.7/100 PYE [95% CI: 0.0, 9.4]). In the Maintenance Study, the EAIRs for

NMSC were also low: 1 subject who received filgotinib 100 mg experienced basal cell carcinoma (EAIR = 0.8/100 PYE [95% CI: 0.0, 4.6]). The expected background rate of NMSC in UC patients based on real-world (claims) data is 0.98 per 100 PYE, 95% CI 0.96-1.01.

However, the filgotinib clinical trial data in the RA and UC populations is considered to be insufficient to assess the potential incidence of NMSC.

With patients with RA and patients with UC being at a higher risk of NMSC, and the long-term effects of immunomodulatory therapy on this risk uncertain, NMSC has been classified as an important potential risk warranting further study as specified in the PV plan of this RMP.

Characterisation of the risk:

The RA ISS is a pooled dataset of Phase 2b and 3 studies in RA of subjects receiving at least 1 dose of filgotinib 100 mg or 200 mg q.d. to support the marketing authorisation application for RA.

In the pooled data that comprises the ISS for RA, the following incidence rates were seen for NMSC.

Table 32: EAIRs of TEAEs of Interest (NMSC) by Preferred Term (Safety Analysis Set, As Treated Subjects)

Treatment-Emergent Adverse Event of Interest	Filgotinib 200 mg q.d.			Filgotinib 100 mg q.d.		
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)
Non-melanoma Skin Cancer	8 (0.4%)	1 (0.2%)	9 (0.4%)	3 (0.2%)	0	3 (0.2%)
	0.3 (0.1,0.5)	0.1 (0.0,0.5)	0.2 (0.1,0.4)	0.2 (0.0,0.4)	0.0 (0.0,5.4)	0.1 (0.0,0.4)

The RA Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg q.d., filgotinib 200 mg q.d. (with or without MTX or csDMARDs). Only the adjudicated positive MACE were included.
AEs of special interest are identified by either lab results, standardised MedDRA queries, or sponsor defined MSTs, or a combination of these methods.
AEs were coded according to MedDRA Version 22.0.
EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact poisson method was used to calculate the 95% CI (Ulm 1990).

UC: In the Induction Studies, the following incidence rates of NMSC were observed:

Table 33: EAIRs of TEAEs of NMSC by Preferred Term, GS-US-418-3898 Induction Studies Cohort 1 (Cohorts A and B Combined; Safety Analysis Set)

Preferred Term	Filgotinib 200 mg (N=507)	Filgotinib 100 mg (N=562)	Placebo (N=279)	EAIR Difference (95% CI)		
	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
Subjects with TEAEs of Non-melanoma Skin Cancers	2/108.6	0/120.2	1/59.2			
	1.8 (0.2,6.7)	0.0 (0.0,3.1)	1.7 (0.0,9.4)	0.2 (-7.7,5.2)	-1.7 (-9.4,1.8)	1.8 (-1.6,6.7)
Basal cell carcinoma	1/108.8	0/120.2	1/59.2			
	0.9 (0.0,5.1)	0.0 (0.0,3.1)	1.7 (0.0,9.4)	-0.8 (-8.5,3.7)	-1.7 (-9.4,1.8)	0.9 (-2.3,5.1)
Bowen's disease	1/108.7	0/120.2	0/59.3			
	0.9 (0.0,5.1)	0.0 (0.0,3.1)	0.0 (0.0,6.2)	0.9 (-5.4,5.1)	0.0 (-6.2,3.1)	0.9 (-2.3,5.1)

Source document: Filgotinib UC ISS, Table 2.2.10.3
EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. TEAEs were defined as any adverse events (AEs) that began on or after study first dose date and up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each PT. PTs were presented by descending order of the total frequencies. AEs of NMSC were defined by the MST list developed by Gilead. Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.

In the Maintenance Study, the following incidence rates of NMSC were observed:

Table 34: EAIRs of TEAEs of Non-Melanoma Skin Cancers by Preferred Term, Cohort 2: GS-US-418-3898 Maintenance Study (Safety Analysis Set)

Preferred Term	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg				Induction Placebo
	Maintenance			Maintenance			Maintenance	Maintenance
	Filgotinib 200 mg (N=202) n/PYE EAIR (95% CI)	Placebo (N=99) n/PYE EAIR (95% CI)	Filgotinib 200 mg vs Placebo EAIR Diff (95% CI)	Filgotinib 100 mg (N=179) n/PYE EAIR (95% CI)	Placebo (N=91) n/PYE EAIR (95% CI)	Filgotinib 100 mg vs Placebo EAIR Diff (95% CI)	Filgotinib 200 mg vs 100 mg EAIR Diff (95% CI)	Placebo (N=93) n/PYE EAIR (95% CI)
Subjects with TEAEs of Non-melanoma Skin Cancers	0/154.0	0/55.3		1/120.1	0/52.3			0/69.0
	0.0	0.0	0.0	0.8	0.0	0.8	-0.8	0.0
	(0.0,2.4)	(0.0,6.7)	(-6.7,2.4)	(0.0,4.6)	(0.0,7.1)	(-6.3,4.6)	(-4.6,1.7)	(0.0,5.3)
Basal cell carcinoma	0/154.0	0/55.3		1/120.1	0/52.3			0/69.0
	0.0	0.0	0.0	0.8	0.0	0.8	-0.8	0.0
	(0.0,2.4)	(0.0,6.7)	(-6.7,2.4)	(0.0,4.6)	(0.0,7.1)	(-6.3,4.6)	(-4.6,1.7)	(0.0,5.3)

Source document: Filgotinib UC ISS, Table 2.2.10.4
EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. TEAEs were defined as any adverse events (AEs) that began on or after study first dose date and up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each PT. PTs were presented by descending order of the total frequencies. AEs of NMSC were defined by the MST list developed by Gilead. Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.

In the integrated data for UC, which includes the subjects treated in Study GS-US-418-3898 and the long-term extension study GS-US-418-3899, the following event rates for NMSC were observed:

Table 35: EAERs of TEAEs of Non-Melanoma Skin Cancers by Preferred Terms, Cohort 3: GS-US-418-3898 and GS-US-418-3899 combined (Safety Analysis Set)

	Non-model-based Descriptive Statistics			Model- based EAER Ratio (95% CI)		
Preferred Term	Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)	Placebo (N=469) (PYE=324.7) n (EAER*)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
Number of Treatment-Emergent Adverse Events of Non-melanoma Skin Cancers #	8 (0.6)	3 (0.8)	1 (0.3)	1.6 (0.2,10.8)	3.6 (0.2,79.2)	0.4 (0.0,4.8)
Basal cell carcinoma #	7 (0.6)	2 (0.5)	1 (0.3)	1.5 (0.2,9.9)	2.4 (0.1,42.1)	0.6 (0.1,4.2)
Bowen's disease	1 (0.1)	0	0	NEst	NEst	NEst
Squamous cell carcinoma of skin	0	1 (0.3)	0	NEst	NEst	NEst

Source document: Filgotinib UC ISS, Table 2.4.2.8
EAER = exposure-adjusted event rate per 100 PYE; EAER* = (number of events/PYE)*100; # Data contributing to the zero event count for a period across all treatment groups were removed from the model based analysis, so that the ratio of EAER could be estimated. NEst = not estimable. TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. AEs of NMSC were defined by the MST list developed by Gilead. Model based EAER ratio and corresponding 95% CI were estimated using GEE model for longitudinal count data including treatment group adjusted for treatment period and patient population (biologic-naïve or biologic-experienced) with an offset of natural log of exposure time.

Risk factors and risk groups:

The risk factors that are generally recognised for NMSC include sun exposure (i.e. UV), immunosuppressive therapies, phototherapy, ionizing radiation, male sex, advanced age, Caucasian race and previous history of NMSC.

Preventability:

Section 4.4 of the SmPC indicates that NMSC has been reported in patients treated with filgotinib. Periodic skin examination during filgotinib treatment is recommended for patients with increased risk of skin cancer.

Impact on the risk-benefit balance of the product:

NMSC is usually curable causing minimal damage. Advanced-stage skin cancers that are located in the head and neck region may require disfiguring surgery. Considering the nature and low incidence of the risk, the benefit-risk balance for filgotinib remains positive in the context of the treated disease.

Public health impact:

Low rates of NMSC, such as that observed in the filgotinib RA and UC clinical trial programs, would not impact the overall benefit-risk balance of the product.

SVII.3.1.2.6 Major Adverse Cardiovascular Events (MACE)

Potential mechanisms:

Uncertainties around the clinical effects of elevated cholesterol in the target population with chronic treatment provide the putative mechanism for including MACE as an important potential risk. Growing evidence suggests that patients with active untreated RA have reduced total cholesterol, LDL, and HDL levels, which are paradoxically associated with increased cardiovascular risk (Myasoedova et al. 2011). In contrast, declines in inflammation may coincide with increases in serum lipid values. The implications of these changes on CV risk, including MACE are unclear, and the relative impact of systemic autoimmune inflammation and dyslipidemia on cardiovascular risk in RA or UC is not fully understood.

Evidence source(s) and strength of evidence:

MACE is considered a class effect of JAK inhibitors.

Filgotinib treatment was associated with dose-dependent increases in total cholesterol and high-density lipoprotein (HDL) levels, while low density lipoprotein (LDL) levels were slightly increased. LDL/HDL ratios were generally unchanged. Lipid changes were observed within the first 12 weeks of filgotinib treatment and remained stable thereafter.

Long-term exposure to increases in blood lipids in the general population would be expected to be associated with adverse CV outcomes including MACE, but published data indicate that they may not be harmful to RA patients as the benefits of suppression of inflammation may outweigh the risk of the lipid changes (Myasoedova et al. 2011).

With RA and UC patients being at a higher risk of CV disease, and the long-term effects of lipid changes on adverse CV outcomes uncertain, MACE has been classified as an important potential risk warranting further study as specified in the PV Plan of this RMP.

Characterisation of the risk:

RA: Exposure-based analysis of the pooled data comprising the ISS for RA did not identify any signals for MACE. The ISS is a pooled dataset of Phase 2b and 3 studies in RA subjects receiving at least 1 dose of filgotinib 100 mg or 200 mg q.d. to support the marketing authorisation application for RA.

In the pooled data that comprises the ISS for RA, the following incidence rates were seen for MACE.

Table 36: EAIRs of TEAEs of Interest (Major Adverse Cardiovascular Events [MACE]) by Preferred Term (Safety Analysis Set, As Treated Subjects)

MACE Category	Filgotinib 200 mg q.d			Filgotinib 100 mg q.d		
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)
Major Adverse Cardiovascular Events [MACE]	13 (0.7%)	6 (1.3%)	19 (0.8%)	13 (0.9%)	0	13 (0.8%)
	0.4 (0.2,0.7)	0.6 (0.2,1.3)	0.5 (0.3,0.7)	0.7 (0.4,1.1)	0.0 (0.0,5.4)	0.6 (0.3,1.1)
Cardiovascular Death	5 (0.3%)	1 (0.2%)	6 (0.3%)	4 (0.3%)	0	4 (0.2%)
	0.2 (0.1,0.4)	0.1 (0.0,0.5)	0.1 (0.1,0.3)	0.2 (0.1,0.5)	0.0 (0.0,5.4)	0.2 (0.1,0.5)
Non-Fatal Myocardial Infarction	2 (0.1%)	2 (0.4%)	4 (0.2%)	5 (0.3%)	0	5 (0.3%)
	0.1 (0.0,0.2)	0.2 (0.0,0.7)	0.1 (0.0,0.3)	0.3 (0.1,0.6)	0.0 (0.0,5.4)	0.2 (0.1,0.6)
Non-Fatal Stroke	7 (0.4%)	3 (0.7%)	10 (0.4%)	4 (0.3%)	0	4 (0.2%)
	0.2 (0.1,0.5)	0.3 (0.1,0.8)	0.2 (0.1,0.5)	0.2 (0.1,0.5)	0.0 (0.0,5.4)	0.2 (0.1,0.5)

The RA Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg q.d., filgotinib 200 mg q.d. (with or without MTX or csDMARDs).
Multiple AEs were counted only once per subject for each treatment period for each PT. PTs were presented by descending order of total frequencies.
MACE were assessed by an independent cardiovascular safety endpoint adjudication committee. Only the adjudicated positive MACE were included.
AEs were coded according to MedDRA Version 22.0.
EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact poisson method was used to calculate the 95% CI (Ulm 1990).

UC: No filgotinib-treated subjects experienced TEAEs of MACE during the Induction Studies (Source document: Filgotinib UC ISS Ad hoc Table 3).

During the Maintenance Study, the EAIRs for TEAEs of MACE were low (1.3 per 100 PYE, 95% CI 0.2-4.7 for filgotinib 200 mg, and 0.8 per 100 PYE, 95% CI 0.0-4.6 for filgotinib 100 mg). In the Maintenance Study, the following EAIRs of treatment-emergent MACE were observed:

Table 37: EAIRs of TEAEs of MACE Cohort 2: GS-US-418-3898 Maintenance Study (Safety Analysis Set)

	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg				Induction Placebo
	Maintenance			Maintenance			Maintenance	Maintenance
MACE Category	Filgotinib 200 mg (N=202) n/PYE EAIR (95% CI)	Placebo (N=99) n/PYE EAIR (95% CI)	Filgotinib 200 mg vs Placebo EAIR Diff (95% CI)	Filgotinib 100 mg (N=179) n/PYE EAIR (95% CI)	Placebo (N=91) n/PYE EAIR (95% CI)	Filgotinib 100 mg vs Placebo EAIR Diff (95% CI)	Filgotinib 200 mg vs 100 mg EAIR Diff (95% CI)	Placebo (N=93) n/PYE EAIR (95% CI)
Subjects with Any Treatment-Emergent MACE	2/154.0	0/55.3		1/120.3	0/52.3			1/68.9
	1.3	0.0	1.3	0.8	0.0	0.8	0.5	1.5
	(0.2,4.7)	(0.0,6.7)	(-5.5,4.7)	(0.0,4.6)	(0.0,7.1)	(-6.3,4.6)	(-3.5,4.0)	(0.0,8.1)
Cardiovascular Death	2/154.0	0/55.3		0/120.4	0/52.3			0/69.0

	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg				Induction Placebo
	Maintenance			Maintenance			Maintenance	Maintenance
MACE Category	Filgotinib 200 mg (N=202) n/PYE EAIR (95% CI)	Placebo (N=99) n/PYE EAIR (95% CI)	Filgotinib 200 mg vs Placebo EAIR Diff (95% CI)	Filgotinib 100 mg (N=179) n/PYE EAIR (95% CI)	Placebo (N=91) n/PYE EAIR (95% CI)	Filgotinib 100 mg vs Placebo EAIR Diff (95% CI)	Filgotinib 200 mg vs 100 mg EAIR Diff (95% CI)	Placebo (N=93) n/PYE EAIR (95% CI)
	1.3	0.0	1.3	0.0	0.0	0.0	1.3	0
	(0.2,4.7)	(0.0,6.7)	(-5.5,4.7)	(0.0,3.1)	(0.0,7.1)	(-7.1,3.1)	(-2.0,4.7)	(0.0,5.3)
Non-fatal Myocardial Infarction	0	0		0	0			0
Non-fatal Stroke	0/154.0	0/55.3		1/120.3	0/52.3			1/68.9
	0.0	0.0	0.0	0.8	0.0	0.8	-0.8	1.5
	(0.0,2.4)	(0.0,6.7)	(-6.7,2.4)	(0.0,4.6)	(0.0,7.1)	(-6.3,4.6)	(-4.6,1.7)	(0.0,8.1)

Source document: Filgotinib UC ISS Ad hoc Table 4
EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. AEs were coded according to MedDRA Version 22.1. TEAEs were defined as any adverse events (AEs) that began on or after study first dose date and up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each PT. PTs were presented by descending order of the total frequencies. An independent adjudication committee reviewed and adjudicated all potential MACE. Only positively adjudicated events were included. Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.

In the integrated data for UC the following exposure-adjusted event rates of TEAEs of MACE were observed:

Table 38: EAERs of TEAEs of MACE, Cohort 3: Studies GS-US-418-3898 and GS-US-418-3899 Combined (Safety Analysis Set)

	Non-model based Descriptive Statistics			Model based EAER Ratio (95% CI)		
MACE Category	Filgotinib 200 mg (N=971) (PYE=1233.9) n(EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n(EAER*)	Placebo (N=469) (PYE=324.7) n(EAER*)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
Number of Treatment-Emergent MACE #	6 (0.5)	2 (0.5)	2 (0.6)	1.1 (0.2,7.3)	1.1 (0.1,10.9)	1.1 (0.2,5.0)
Cardiovascular Death	4 (0.3)	0	0	NEst	NEst	NEst
Non-fatal Myocardial Infarction	1 (0.1)	0	0	NEst	NEst	NEst
Non-fatal Stroke #	1 (0.1)	2 (0.5)	2 (0.6)	0.2 (0.0,2.6)	0.8 (0.1,8.4)	0.2 (0.0,1.7)

Source document: Filgotinib UC ISS Ad hoc Table 5
EAER = exposure-adjusted event rate per 100 PYE; EAER* = (number of events/PYE)*100; GEE = generalized estimating equations; NEst = not estimable; PYE = patient-years of exposure. # Data contributing to the zero event count for a period across all treatment groups were removed from the model based analysis, so that the ratio of EAER could be estimated. AEs were coded according to MedDRA Version 22.1. An independent adjudication committee reviewed and adjudicated all potential MACE. Only positively adjudicated events were included. Model based EAER ratio and corresponding 95% CI were estimated using a GEE model for longitudinal count data including treatment group adjusted for treatment period and patient population (biologic naïve or biologic-experienced) with an offset of natural log of exposure time.

Risk factors and risk groups:

Patients with RA have a substantially elevated risk of cardiovascular morbidity and mortality. CV disease risk in older patients (≥75) with RA has been reported to be more than 3-fold the Framingham-predicted risk for the general population (Crowson et al. 2012), and female patients

with RA have demonstrated a 2-fold higher risk of myocardial infarction compare with female patients without RA (Solomon et al. 2003). The increased risk of CV disease in the RA population cannot be entirely explained by traditional cardiovascular risk factors, thus indicating that RA-specific characteristics, especially systemic inflammation and disease activity, may be associated with increased cardiovascular risk. Traditional CV risk factors such as smoking, dyslipidemia, obesity, hypertension, diabetes mellitus, age and prior CV events may also apply to patients with RA. As the number of patients in whom MACE has been identified in clinical trials remains very low, no specific risk factors for MACE have been identified with filgotinib.

UC is associated with an increased risk of coronary artery disease, myocardial infarction, cerebrovascular ischemic events, and mesenteric ischemia compared to those without UC despite the lower prevalence of classical CV risk factors in UC population. The increased risk was related to disease severity/activity with highest risk during flares and periods of persistent activity. The increased risk may be more pronounced in women compared to men, and in younger patients compared to elderly patients (Kristensen et al. 2013; Singh et al. 2014; Schicho et al. 2015; Feng et al. 2017). The reason for the increased risk is multifactorial, including pathological processes associated with UC (e.g. increase in proinflammatory cytokines and C-reactive protein), biological changes associated with UC (e.g. elevation of coagulation factors, changes in lipid profiles and intestinal microbiome), and short- and long-term medications used in the treatment of UC.

Preventability:

Section 4.2 of the SmPC recommends a dose adjustment in adults at increased risk for MACE. Section 4.4 of the SmPC provides advice that the risk factors for MACE should be managed in accordance with standard clinical practice as well as on administering filgotinib to patients with CV risk factors.

Additional risk minimisation materials (HCP guide) provide advice on the management of CV disease risk. The PAC provides information on the management of lipids, a risk factor for CV disease.

Impact on the risk-benefit balance of the product:

The low rates of MACE observed in the filgotinib RA clinical trial program are not considered to impact the overall benefit-risk balance of the product. Considering the overall burden of the disease, the benefit-risk balance for filgotinib remains positive.

Public health impact:

CV disease is a major public health issue and is among the leading causes of morbidity and mortality worldwide. At a very low rates such as that observed in the filgotinib clinical trial program, the public health impact of MACE would be low.

SVII.3.1.2.7 Hyperlipidaemia

Potential mechanisms:

Published clinical data indicate that altered activity in lecithin-cholesterol acyltransferase (LCAT) and cholesterol esterification represent an important regulatory step that is modified by inflammation and potentially reversed by JAK inhibition (Charles-Schoeman et al. 2015). Data suggest that low cholesterol observed in patients with active RA may in part be driven by increases in cholesterol ester catabolism. The JAK inhibitor tofacitinib has been associated with decreases in cholesterol ester catabolism, resulting in increased cholesterol levels toward the range found in healthy subjects.

Evidence source(s) and strength of evidence:

In clinical trials, filgotinib treatment was associated with dose-dependent increases in total cholesterol and high-density lipoprotein (HDL) levels, while low density lipoprotein (LDL) levels were slightly increased. LDL/HDL ratios were generally unchanged. Lipid changes were observed within the first 12 weeks of filgotinib treatment and remained stable thereafter.

As the long-term effects of lipid changes on adverse CV outcomes is uncertain, hyperlipidaemia has been classified as an important potential risk warranting further study as specified in the PV Plan of this RMP.

Characterisation of the risk:

RA: Exposure-based analysis of the pooled data comprising the ISS did not identify any signals for hyperlipidaemia. The ISS is a pooled dataset of Phase 2b and 3 studies in RA subjects receiving at least 1 dose of filgotinib 100 mg or 200 mg q.d. to support the marketing authorisation application for RA.

In the pooled data that comprises the ISS for RA, the following incidence rates were seen for hyperlipidaemia-related TEAEs:

Table 39: EAIRs for Hyperlipidemia related TEAEs in the As Treated Population for the RA ISS.

	Filgotinib 200 mg			Filgotinib 100 mg		
Preferred Term	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)
Hyperlipidaemia	23 (1.3%) 0.8 (0.5,1.1)	3 (0.7%) 0.3 (0.1,0.8)	26 (1.1%) 0.6 (0.4,0.9)	13 (0.9%) 0.7 (0.4,1.1)	1 (0.7%) 1.5 (0.0,8.2)	14 (0.9%) 0.7 (0.4,1.2)
Type V hyperlipidaemia	1 (<0.1%) 0.0 (0.0,0.2)	1 (0.2%) 0.1 (0.0,0.5)	2 (<0.1%) 0.0 (0.0,0.2)	0 0.0 (0.0,0.2)	0 0.0 (0.0,5.4)	0 0.0 (0.0,0.2)
Lipids increased	1 (<0.1%) 0.0 (0.0,0.2)	0 0.0 (0.0,0.4)	1 (<0.1%) 0.0 (0.0,0.1)	0 0.0 (0.0,0.2)	0 0.0 (0.0,5.4)	0 0.0 (0.0,0.2)
Blood cholesterol increased	13 (0.7%) 0.4 (0.2,0.7)	17 (3.8%) 1.6 (0.9,2.6)	30 (1.3%) 0.7 (0.5,1.1)	3 (0.2%) 0.2 (0.0,0.4)	0 0.0 (0.0,5.4)	3 (0.2%) 0.1 (0.0,0.4)

Preferred Term	Filgotinib 200 mg			Filgotinib 100 mg		
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)
Hyper-cholesterolaemia	45 (2.5%) 1.5 (1.1,2.0)	23 (5.1%) 2.2 (1.4,3.3)	68 (3.0%) 1.7 (1.3,2.1)	22 (1.5%) 1.1 (0.7,1.7)	8 (5.2%) 11.7 (5.1,23.1)	30 (1.8%) 1.5 (1.0,2.1)
Dyslipidaemia	42 (2.3%) 1.4 (1.0,1.9)	16 (3.6%) 1.5 (0.9,2.5)	58 (2.6%) 1.4 (1.1,1.9)	23 (1.5%) 1.2 (0.7,1.8)	3 (2.0%) 4.4 (0.9,12.8)	26 (1.6%) 1.3 (0.8,1.9)

The RA Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg q.d., filgotinib 200 mg q.d., (with or without MTX or csDMARDs).
Adverse events were coded according to MedDRA Version 22.0.
Treatment-emergent events began on or after the first dose date of filgotinib 100 mg q.d. or filgotinib 200 mg q.d., and no later than the earlier date of either 30 days after the last dose date, or the first dose date of the switched treatment minus 1 day.
Multiple AEs were counted only once per subject for each treatment period for each Preferred Term (PT).
EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact poisson method was used to calculate the 95% CI (Ulm 1990).

UC: In the Induction Studies, the following incidence rates for hyperlipidemia related TEAEs were observed:

Table 40: EAIRs for TE Hyperlipidemia Related Events by Preferred Term, GS-US-418-3898 Induction Studies Cohort 1 (Cohorts A and B Combined; Safety Analysis Set)

Preferred Term	Filgotinib 200 mg	Filgotinib 100 mg	Placebo	EAIR Difference (95% CI)		
	(N=507) n/PYE EAIR (95% CI)	(N=562) n/PYE EAIR (95% CI)	(N=279) n/PYE EAIR (95% CI)	Filgotinib 200 mg vs. Placebo	Filgotinib 100 mg vs. Placebo	Filgotinib 200 mg vs. 100 mg
Hyperlipidaemia	No subjects reported this PT during Induction Studies					
Type V hyperlipidaemia	No subjects reported this PT during Induction Studies					
Lipids increased	No subjects reported this PT during Induction Studies					
Blood cholesterol increased	2/108.7 1.8 (0.2,6.6)	1/120.1 0.8 (0.0, 4.6)	0/59.3 0.0 (0.0,6.2)	1.8 (-4.6, 6.6)	0.8 (-5.4, 4.6)	1.0 (-3.1, 5.9)
Hyper-cholesterolaemia	3/108.5 2.8 (0.6,8.1)	1/120.0 0.8 (0.0, 4.6)	0/59.3 0.0 (0.0,6.2)	2.8 (-3.8, 8.1)	0.8 (-5.4, 4.6)	1.9 (-2.5, 7.3)
Dyslipidaemia	2/108.4 1.8 (0.2, 6.7)	2/120.0 1.7 (0.2,6.0)	0/59.3 0.0 (0.0,6.2)	1.8 (-4.6, 6.7)	1.7 (-4.7, 6.0)	0.2 (-4.5, 5.2)

Source document: Filgotinib UC ISS, Table 2.1.7
EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. Adverse events were coded according to the MedDRA Version 22.1. Treatment-emergent adverse events were defined as any adverse events (AEs) that began on or after the study first dose date up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each Preferred Term. Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.

In the Maintenance Study, the following incidence rates for hyperlipidemia related TEAEs were observed:

Table 41: EAIRs of TE for Hyperlipidemia Related Events by Preferred Term, GS-US-418-3898, Cohort 2: Maintenance Study (Safety Analysis Set)

	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg				Induction Placebo
	Maintenance			Maintenance			Maintenance	Maintenance
Preferred Term	Filgotinib 200mg (N=202) n/PYE EAIR (95% CI)	Placebo (N=99) n/PYE EAIR (95% CI)	Filgotinib 200 mg vs. Placebo EAIR Diff (95% CI)	Filgotinib 100mg (N=179) n/PYE EAIR (95% CI)	Placebo (N=91) n/PYE EAIR (95% CI)	Filgotinib 100 mg vs. Placebo EAIR Diff (95% CI)	Filgotinib 200 mg vs. 100 mg EAIR Diff (95% CI)	Placebo (N=93) n/PYE EAIR (95% CI)
Hyperlipidaemia	1/153.6 0.7 (0.0, 3.6)	1/55.0 1.8 (0.0, 10.1)	-1.2 (-9.5, 2.3)	1/120.3 0.8 (0.0, 4.6)	1/51.8 1.9 (0.0, 10.8)	-1.1 (-10.0, 3.1)	-0.2 (-4.0, 2.9)	0/69.0 0.0 (0.0,5.3)
Type V hyperlipidaemia	No subjects reported this PT during the Maintenance Study							
Lipids increased	No subjects reported this PT during the Maintenance Study							
Blood cholesterol increased	3/152.6 2.0 (0.4,5.7)	0/55.3 0.0 (0.0, 6.7)	2.0 (-4.9, 5.7)	0/120.4 0.0 (0.0, 3.1)	0/52.3 0.0 (0.0, 7.1)	0.0 (-7.1, 3.1)	2.0 (-1.5, 5.7)	0/69.0 0.0 (0.0,5.3)
Hyper-cholesterolaemia	1/154.0 0.6 (0.0, 3.6)	0/55.3 0.0 (0.0,6.7)	0.6 (-6.0, 3.6)	0/120.4 0.0 (0.0, 3.1)	0/52.3 0.0 (0.0, 7.1)	0.0 (-7.1, 3.1)	0.6 (-2.5, 3.6)	0/69.0 0.0 (0.0,5.3)
Dyslipidaemia	1/153.9 0.6 (0.0, 3.6)	0/55.3 0.0 (0.0, 6.7)	0.6 (-6.0, 3.6)	0/120.4 0.0 (0.0,3.1)	0/52.3 0.0 (0.0, 7.1)	0.0 (-7.1, 3.1)	0.6 (-2.5, 3.6)	0/69.0 0.0 (0.0,5.3)

Source document: Filgotinib UC ISS, Table 2.1.8
EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TEAE = treatment-emergent adverse event. AEs were coded according to the MedDRA Version 22.1. Treatment-emergent adverse events were defined as any adverse events (AEs) that began on or after the study first dose date up to 30 days after the last dose date within the same study or 1 day before the first dose date of next study, whichever was earlier. Multiple AEs were counted only once per subject for each Preferred Term. Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.

In the integrated data for UC, the following event rates for hyperlipidemia related TEAEs were observed:

Table 42: EAERs of Treatment-Emergent Adverse Events for hyperlipidemia related events by Preferred Term, Cohort 3: GS-US-418-3898 and GS-US-418-3899 Combined (Safety Analysis Set)

Preferred Term	Non-model based Descriptive Statistics			Model based EAER Ratio (95% CI)		
	Filgotinib 200 mg (N=971) (PYE=1233.9) n(EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n(EAER*)	Placebo (N=469) (PYE=324.7) n(EAER*)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
Hyperlipidaemia#	5 (0.4)	2 (0.5)	2 (0.6)	0.6 (0.1, 3.1)	1.7 (0.2, 15.3)	0.4 (0, 3.4)
Type V hyperlipidaemia	No subjects reported this PT					
Lipids increased	No subjects reported this PT					
Blood cholesterol increased #, $	5 (0.4)	1 (0.3)	0	NEst	NEst	3.0 (0.4, 24.4)
Hyper-cholesterolaemia #, $	15 (1.2)	3 (0.8)	0	NEst	NEst	2.3 (0.7, 8.0)
Dyslipidaemia	3 (0.2)	2 (0.5)	0	NEst	NEst	NEst

Source document: Filgotinib UC ISS, Table 2.4.2.1
EAER = exposure-adjusted event rate per 100 PYE; EAER* = (number of events /PYE)*100; # Data contributing to the zero event count for a period across all treatment groups were removed from the model based analysis, so that the ratio of EAER could be estimated. $ Data contributing to the zero event count for only one treatment group were removed from the model based analysis, so that the ratio of EAER for the other 2 treatment groups having events could be estimated. NEst = not estimable. AEs were coded according to MedDRA Version 22.1. Model based EAER ratio and corresponding 95% CI were estimated using generalised estimating equations (GEE) model for longitudinal count data including treatment group adjusted for treatment period and patient population (biologic-naïve or biologic-experienced) with an offset of natural log of exposure time.

Risk factors and risk groups:

Modifiable risk factors for hyperlipidemia include a diet high in saturated fats, physical inactivity, smoking and obesity. Other risk factors include biliary obstruction, chronic kidney disease, type 2 diabetes mellitus, high blood pressure, and hypothyroidism. Familial hypercholesterolemia (a monogenic disorder) is estimated to occur in 1:500 individuals in the general population. RA itself is an established risk factor for dyslipidemia.

Preventability:

No known preventable measures. Sections 4.2 and 4.4 of the SmPC provide guidance for the monitoring of blood lipids during filgotinib treatment. Patients should be managed according to standard clinical guidelines for the management of hyperlipidaemia.

Impact on the risk-benefit balance of the product:

As observed increases in total cholesterol, HDL, and LDL in Phase 3 filgotinib studies were numerically small, and considering the overall burden of the disease, the overall benefit-risk balance for filgotinib remains positive.

Public health impact:

The impact of hyperlipidaemia for the patient can be mild (requiring medication) to severe due to the potential development of cardiovascular disease. Small increases in total cholesterol, HDL, and LDL such as that seen in Phase 3 filgotinib studies, would have a low public health impact.

SVII.3.1.2.8 Varicella Zoster

Potential mechanisms:

JAK/STAT pathway is involved in the signaling of numerous interferons, interleukins and cytokines that are involved in the immuno-inflammatory response. In addition, the underlying disease and concomitant use of immunosuppressive therapies may increase the risk of complications of primary varicella zoster infection in RA patients.

Evidence source(s) and strength of evidence:

Primary varicella zoster virus (VZV) infection in adults is rare as most patients are exposed to the virus in childhood or have been vaccinated. No signal for VZV infection has been detected in the filgotinib RA clinical trial program.

As RA patients with no history of prior infection who are being treated with JAK inhibitors or other immunomodulatory drugs are at a higher risk of complications if a primary infection occurs, varicella zoster has been classified as an important potential risk warranting further study as specified in the PV plan of this RMP.

Characterisation of the risk:

RA: Analysis of data from the ISS has not identified any signals for serious VZV infection. In the pooled data that comprises the ISS for RA, 2 serious VZV cases were identified, 1 with a fatal outcome. Both cases were reported in the 100 mg filgotinib + csDMARDs group. For both cases, the subjects were receiving concurrent MTX therapy. Neither of the 2 subjects had been reported as having received vaccination for VZV.

UC: In the UC clinical program, no TEAE of VZV infection was reported for filgotinib-treated subjects.

Risk factors and risk groups:

Patients with RA are at increased risk of developing infections, compared to those without RA. The reasons are multifactorial, including a poorly functioning immune system and concomitant use of immunosuppressant medications such as glucocorticoids. Adult RA patients may be at risk of complications of primary VZV infection, of which pneumonia is the most common complication of primary VZV infection in adults.

Preventability:

Preventative measures for patients with no history of VZV infection and who have not been vaccinated include testing for varicella zoster IgG and utilisation of prophylactic varicella vaccination, in accordance with local vaccination guidelines. Prescribers can also consider utilisation of post-exposure prophylaxis or treatment with antivirals such as acyclovir or valaciclovir, or with varicella zoster immune globulin product.

Impact on the risk-benefit balance of the product:

Two cases of serious VZV infection have been reported during treatment with filgotinib in the RA clinical program. No cases of VZV infection have been reported during treatment with filgotinib in the UC Induction and Maintenance studies. Considering the overall burden of the disease and the quality of life in RA and UC, and the low incidence of VZV seen in the clinical trial program, the overall benefit-risk balance for filgotinib remains positive.

Public health impact:

Low, due to widespread childhood exposure and vaccination, the available prophylactic vaccination, immunity screening and post-exposure prophylaxis and treatment availability.

SVII.3.1.2.9 Fractures

Potential mechanisms:

In preclinical studies conducted in rat collagen-induced arthritis model with established arthritis, filgotinib demonstrated a dose-dependent reduction in bone erosion. No safety concern suggestive of a risk of fractures was observed in any of the preclinical studies conducted with filgotinib. No risk of fractures was detected in the clinical development program for filgotinib across all studies indications.

Evidence source(s) and strength of evidence:

As part of a regulatory procedure (Tofacitinib - XELJANZ (CAP) - EMEA/H/C/ 004214/II/0044), based on the final results from study A3921133, the label for JAKi tofacitinib was updated to include warnings and safety data concerning fractures.

Various studies have shown that RA is a risk factor for bone fracture in both men and women, with comparable risks of fractures at the vertebral body and hip (Hooyman et al. 1984; Michel et al. 1993; Kröger et al. 1994; West et al. 1994; Lane et al. 1995; Haugeberg et al. 2000; Staa et al. 2006).

In RA, local and systemic bone loss develop, which require treatments that not only influence inflammation but also maintain or even restore bone mass (Cohen et al. 2008; Schett and Gravallese 2012; Zerbini et al. 2017). Various trials conducted on JAKis to evaluate bone homeostasis have suggested that JAKis may pose a beneficial impact on bone metabolism (Villarino et al. 2017).

A review of the literature also suggests that there is an association between IBD and the risk of developing osteoporotic fractures (staa et al. 2003; Hidalgo et al. 2018).

In addition to the aforementioned risks of RA and IBD for fractures, glucocorticoids are the most frequently noted causative drugs for osteoporotic fractures. However, fractures have been associated with several commonly used drugs including but not limited to thyroid hormone, oral anticoagulants, proton pump inhibitors, thiazolidinediones, selective serotonin reuptake inhibitors, and anticonvulsants (Mazziotti et al. 2010).

Incidence rates among RA and UC patients tend to be greater than cited general population incidence of fractures, which is estimated to be 1.23 per 100 PY (Bergh et al. 2020). Pooled statistics from meta-analyses signaled a more than 2–fold increase risk of fractures in RA, with a pooled overall fracture incidence rate of 3.30 per 100 PY (Jin et al. 2018) and a 2.25 greater risk of fracture than the general population (Xue et al. 2017).

With patients with RA and patients with UC being at a higher risk of fractures, and fractures having been associated with some JAK inhibitors, fractures have been classified as an important potential risk warranting further study as specified in the PV plan of this RMP.

Characterisation of the risk:

An evaluation of clinical trial data across both RA and UC subjects showed that EAIRs (95% CI) were comparable between filgotinib-treated subjects across all doses and the comparator product (placebo or active) for all reported fracture events. Across all reported fractures, the absolute numbers were small and did not suggest any clustering to fractures to any specific type or to any specific anatomic location.

Xue et al., in a meta-analysis of 13 studies showed a significant higher risk of bone fracture in patients with RA than in patients without RA (pooled risk ratio [RR]=2.25, 95% CI: 1.76-2.87). Sub-group analyses showed that both female and male patients with RA had an increased risk of fracture when compared with female and male patients without RA (Xue et al. 2017). In a systematic review and meta-analysis Jin et al. estimated the pooled IR of overall fractures in RA patients. They estimated a pooled IR of 330.0 (95% CI: 183.9-592.1) per 10,000 PYs for overall fractures in RA patients based on data from 10 cohort studies. Individual IR estimates from these 10 studies ranged from 69.4 to 862.7 per 10,000 PYs (Jin et al. 2018). Patients with RA are at risk of osteoporosis and osteoporotic fractures (Wright et al. 2011). Clinical studies have shown that the incidence of osteoporosis among RA patients is 1.9 times higher than among non-RA patients (Lee et al. 2012). Additionally, chronic inflammation, physical inactivity and glucocorticoids mediating the increased osteoporosis further predisposes an RA patient to develop a fracture (Ozen et al. 2019).

A review of the literature also suggests that there is an association between IBD and the risk of developing osteoporotic fractures. In a meta-analysis based on 7 observational studies conducted by Hidalgo et al., the pooled OR was 1.32 (95% CI: 1.20-1.45) for patients with IBD when compared with subjects without IBD (Hidalgo et al. 2019). Van Staa et al., in a nested case-control study showed an increased risk of vertebral fracture (OR: 1.72; 95% CI: 1.13-2.61) and hip fracture (OR: 1.59; 95% CI: 1.14-2.23) in patients with IBD. In the study, the risk of hip

fracture was greater in patients with CD (OR: 1.86; 95% CI: 1.08-3.21) compared with UC (OR: 1.40; 95% CI: 0.92-2.13). The disease severity, assessed by the number of symptoms, predicted fracture even after adjusting for corticosteroid use (OR: 1.46; 95% CI: 1.04-2.04). Only 13% of patients with IBD who had already sustained a fracture were on any form of antifracture treatment (Staa et al. 2003).

Risk factors and risk groups:

Overall, results suggest that patients across both diseases, RA and UC, have a greater risk of fracture compared to the general population. The most marked risk was observed in the RA population, which had the highest incidence and greatest RR compared to the general population among studies reviewed across both diseases, followed by UC.

Across diseases, fracture risk was most commonly reported for vertebral and hip fractures, with increased risk observed among these fracture types across diseases (as high as five–fold odds versus the general population in the case of hip fracture in UC) (Komaki et al. 2019). Comparatively less data was reported on other fracture types, including pelvic, humeral, femoral, and wrist.

Reporting on DMARD and biologic use was more frequent in RA than UC. The specific analyses conducted varied, thereby preventing direct comparison of outcomes. Generally, DMARD use was associated with reduced incidence rates, although a South Korean database analysis found higher incidence rates in TNF inhibitor, abatacept, and tocilizumab RA users compared to the general population (Shin et al. 2020). Similarly, a large United States (US) claims analysis found relatively high incidence rates of non–vertebral fractures in TNF inhibitor RA users, although non–users experienced very similar fracture rates (Shao et al. 2021).

Preventability:

No data are available to identify specific measure that can be used to prevent the occurrence of fractures while patient is on filgotinib therapy.

Impact on the risk-benefit balance of the product:

Overall, the comprehensive review of fracture data across different sources did not suggest any risk of fractures with filgotinib therapy. On the contrary, the mechanistic evidence and data from non-clinical studies show that filgotinib may have a positive effect on bone homeostasis. Considering the overall burden of the disease, the benefit-risk balance for filgotinib remains positive.

Public health impact:

Fractures may happen in individuals at any age. However, the fracture type and anatomic location show high variability depending on different factors, mainly related to individual bone quality and the nature of the potential trauma (Bergh et al. 2020). Given the comparable occurrence of

fractures in both the filgotinib group and the comparator group shown in the filgotinib clinical trial program, the public health impact of fractures would be low.

SVII.3.1.3 Missing Information

SVII.3.1.3.1 Use in Patients with Evidence of Untreated Chronic Infection With Hepatitis B or C

Anticipated risk/consequence of the missing information:

Subjects with active hepatitis B or hepatitis C disease were excluded from filgotinib clinical trials. Subjects with evidence of prior exposure to hepatitis B (hepatitis B core antibody positive, surface antigen negative and hepatitis B DNA negative) and/or hepatitis C (hepatitis C antibody positive) but without active disease were allowed to enroll in Phase 3 trials, with the requirement to undergo viral load testing every 3 months. It remains unclear whether filgotinib affects hepatitis B and/or hepatitis C viral activity in patients with RA or UC, due to the immunomodulatory potential of JAK inhibitors. The safety profile in this population will be derived from routine pharmacovigilance activities.

SVII.3.1.3.2 Effect on Vaccination Efficacy

Anticipated risk/consequence of the missing information:

It is unknown if the immunomodulatory action of filgotinib will reduce the efficacy of vaccines administered during therapy. Live/attenuated vaccines are not recommended for use during filgotinib treatment, however, the efficacy of other commonly used vaccines, such as the annual influenza vaccine, may be impacted. EULAR provides recommendations of vaccination in adult patients with autoimmune inflammatory rheumatic diseases (Assen et al. 2011), and the European Crohn's and Colitis Organization (ECCO) provides recommendations of vaccination in adult patients with IBD (Rahier et al. 2014). The SmPC advises that immunisations be updated prior to initiating treatment with filgotinib. As specific clinical measures to manage vaccination have become fully integrated into standard clinical practice, the potential impact of this safety concern is considered to be low. Information on the effect on vaccination efficacy may be gained from routine pharmacovigilance activities.

SVII.3.1.3.3 Use in the Very Elderly (>75 Years)

Anticipated risk/consequence of the missing information:

There was limited safety data for the very elderly (>75 years) exposed to filgotinib in the filgotinib in the RA clinical program. Although the low number of the very elderly subjects in each treatment group precluded a meaningful analysis, no specific signals for adverse events of interest including MACE, serious infections, HZ, active TB, opportunistic infections (OIs), malignancies excluding NMSC, NMSC, and GI perforation were identified in this population. However, there was a higher incidence of serious infections in this population. There were no very elderly (>75 years) subjects who participated in the UC clinical program.

Elderly patients are particularly subject to polypharmacy. However, filgotinib, primarily metabolised by carboxylesterase (CES)2 and CES1, is not a clinically relevant inhibitor or inducer of enzymes or transporters commonly involved in drug interactions such as cytochrome P450 (CYP) enzymes and UDP-glucuronosyltransferases (UGT). Furthermore, age does not have a clinically relevant effect on the pharmacokinetics (AUC and C_{max}) of filgotinib or its primary metabolite (GS-829845). Therefore, there seems no special concern for drug interaction in this population.

The prevalence of RA is highest at 70 years of age and over (Arthritis 2019). Thus, it is anticipated that in everyday clinical practice, very elderly patients will comprise a considerable component of the targeted population for filgotinib treatment. Elderly patients usually have more comorbidities. A recent epidemiologic analysis based on a US medical claims database in RA patients indicated an upward trend in incidence rates with age for the following events: lymphoma, GI perforation, HZ, OIs, and VTE (Gilead data on file). A meta-analysis was recently conducted in biologic-treated patients with inflammatory diseases including RA. The analysis showed the increased risks of infections (OR of 2.28, 95% CI 1.57-3.31) and malignancies (OR of 3.07, 95% CI 1.98-4.62) in older patients (≥60 years) compared to younger ones (Borren and Ananthakrishnan 2019).

Although there has been an increased incidence of UC in different age groups, the majority of patients with UC are in the age group of 30 to 40 years at diagnosis (Cosnes et al. 2011).

Certain publications indicate that a second incidence peak occurs in an older age group (Loftus et al. 2007). Patients 75 years and older are not included in the indication for UC. Section 4.2 of the SmPC states that filgotinib is not recommended in patients with UC aged 75 years and older, as there is no data in this population.

It remains unclear whether the filgotinib safety profile in patients with RA will be impacted by very elderly age in light of the limited exposure data. The safety data in this population will be derived from routine and additional pharmacovigilance activities (non-interventional post-authorisation safety study of filgotinib in patients with RA in European registries).

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table 43: Summary of Safety Concerns

Important identified risk	Serious and opportunistic infections
	Herpes zoster
Important potential risk	Embryolethality and teratogenicity
	Malignancy
	Venous thromboembolism (DVT and PE)
	Gastrointestinal (GI) perforation
	Non-melanoma skin cancer (NMSC)
	MACE
	Hyperlipidemia
	Varicella zoster
	Fractures
Missing information	Use in patients with evidence of untreated chronic infection with hepatitis B or C
	Effect on vaccination efficacy
	Use in the very elderly (>75 years)

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

III.1.1 Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

III.1.1.1 Specific Adverse Reaction Follow-up Questionnaires

For the safety concerns for filgotinib, specific adverse reaction follow-up questionnaires will be used to obtain comprehensive information for spontaneously reported adverse events (Table 44). Copies of the follow-up questionnaires are provided in Annex 4.

Table 44: Specific Adverse Reaction Follow-up Questionnaires

Name of Questionnaire	Associated Safety Concern	Description
Pregnancy Report Form Pregnancy Outcome Form	Embryolethality and teratogenicity (Important potential risk)	The questionnaires are designed to obtain information on contraceptive measures used, relevant medical history and risk factors, relevant concomitant medications, and the outcome of the pregnancy.
Malignancy	Malignancy (Important potential risk)	The questionnaire is designed to obtain details of clinical presentation, relevant medical history and risk factors, relevant concomitant medications, laboratory data, diagnostic procedures, treatment and outcome of the event.
Serious and opportunistic infections	Serious and opportunistic infections (Important identified risk)	
Venous thromboembolism	Venous thromboembolism (Important potential risk)	
Gastrointestinal perforation	GI perforation (Important potential risk)	
Non-Melanoma Skin Cancer	Non-melanoma skin cancer (Important potential risk)	
MACE	MACE (Important potential risk)	
Dyslipidemia	Hyperlipidemia (Important potential risk)	
Varicella zoster virus (VZV) infection: Primary varicella (Chicken pox) or Herpes zoster (Shingles)	Herpes zoster (Important identified risk), Primary varicella zoster infection (Important potential risk)	

III.1.1.2 Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 45: Ongoing and Planned Additional Pharmacovigilance Activities

Study Title	Rationale and Study Objectives	Study Design and Study Populations	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None proposed.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None proposed.				
Category 3 - Required additional pharmacovigilance activities				
GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA	*Safety concern addressed:* Serious and opportunistic infections, Herpes Zoster (Important identified risks) Malignancy, Venous thromboembolism, GI perforation, MACE, NMSC, Hyperlipidaemia, Varicella zoster, Fractures (Important potential risks) Use in the very elderly (>75 years) (Missing information) *Objectives:* to evaluate the long-term safety and tolerability of filgotinib for the treatment of RA in subjects who received treatment in the parent studies	Phase 3 dose-blinded long-term extension study Adult males and females with RA who have completed 1 of the Phase 3 parent studies	Submission of final study report	Q2 2026
GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries	*Safety concern addressed:* Serious and opportunistic infections, Herpes Zoster (Important identified risks) Malignancy, Venous thromboembolism, GI perforation, MACE, NMSC, Hyperlipidaemia, Varicella zoster, Fractures (Important potential risks)	Non-interventional, post-authorisation, prospective cohort study with secondary use of data collected by European registries including the ARTIS registry (Swe), BIOBADASER (ES), the BSRBR-RA (UK), DANBIO (DK), and RABBIT (DE). The study population will include all RA patients	Interim reports Final report	2 yearly Q2 2031

Study Title	Rationale and Study Objectives	Study Design and Study Populations	Milestones	Due Dates
	Use in the very elderly (>75 years), (Missing information) *Objectives:* To monitor the incidence rate, and better characterise the risks of Serious and opportunistic infections, Herpes zoster, Malignancy, Venous thromboembolism, GI perforation, MACE, NMSC, Hyperlipidaemia, Varicella zoster, Fractures, and all-cause mortality in a real-world population.	who initiate treatment with filgotinib and are enrolled in each registry, following approval in Europe and commercial availability in the respective country until the end of the study period. To provide context for the incidence rates of the safety events of interest observed in patients initiating treatment with filgotinib, comparator cohorts will also be used.		
GLPG0634-CL-408 (GS-EU-417-9050, GS-EU-417-9051, GS-EU-417-9052, GS-EU-417-5884, GS-EU-417-5885) Non-interventional post-authorisation cohort safety study evaluating the effectiveness of the additional RMMs for filgotinib (Jyseleca®) use in patients with moderate to severe active RA within European registries.	*Objective*: To evaluate the effectiveness of the additional RMMs for filgotinib use in RA patients who initiate treatment with filgotinib.	Drug utilisation study (DUS) using a non-interventional follow-up cohort design with secondary use of European registries (ARTIS, BIOBADASER, BSRBR-RA, DANBIO, RABBIT). The study population will include all patients with moderate to severe active RA identified from the 5 registries who initiate treatment with filgotinib following approval in Europe, launch/commercial availability for the treatment of RA and implementation of the additional RMMs in each country.	Interim study report (Year 2) Final study report (Year 4)	Q1 2025 Q2 2027
GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with UC	*Safety concern addressed:* Serious and opportunistic infections, Herpes Zoster (Important identified risks) Malignancy, Venous thromboembolism, GI perforation, MACE,	Long-term extension study to evaluate the safety of filgotinib administered to subjects with UC, who have completed or met protocol specified efficacy	Submission of final CSR	Q4 2027

Study Title	Rationale and Study Objectives	Study Design and Study Populations	Milestones	Due Dates
	NMSC, Hyperlipidaemia, Varicella zoster, Fractures (Important potential risks) *Objectives:* To observe the long-term safety of filgotinib in subjects who have completed or met protocol specified efficacy discontinuation criteria in a prior Gilead-sponsored filgotinib treatment study in UC.	discontinuation criteria in a prior Gilead-sponsored filgotinib treatment study in UC (Study GS-US-418-3898).		
GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, Post-authorisation, Prospective Safety Study of Filgotinib Patients with Moderately to Severely Active UC: a European multi registry-based study	*Safety concern addressed:* Serious and opportunistic infections, Herpes Zoster (Important identified risks), Malignancy, Venous thromboembolism, GI perforation, MACE, NMSC, Hyperlipidaemia, Varicella zoster, Fractures (Important potential risks) *Objectives:* To monitor the incidence rate, and better characterise the risks of Serious and opportunistic infections, Herpes zoster, Malignancy, Venous thromboembolism, GI perforation, MACE, NMSC, Hyperlipidaemia, Varicella zoster, Fractures, and all-cause mortality in a real-world UC population.	Non-interventional, post-authorisation, prospective multicountry, registry-based safety cohort study with secondary use of data collected from 3 European IBD registries. The study population will include male or female patients (18+ years of age) with prevalent or incident UC who initiate treatment with filgotinib or other drug classes of interest used for UC treatment and who are enrolled in the European IBD registries from which data are collected following commercial availability of the treatment for UC in each country until the end of the study period. To provide context for the incidence rates of the safety events of interest observed in patients initiating treatment with filgotinib, comparator cohorts will also be used.	Interim report Annual progress reports Final report	Approximately 5 years after start of data collection Yearly April 2032, 12 months after the end of data collection in all participating countries

Study Title	Rationale and Study Objectives	Study Design and Study Populations	Milestones	Due Dates
GLPG0634-CL-417 (GS-EU-418-5981) Non-interventional, post-authorisation prospective cohort study evaluating the effectiveness of the additional RMMs for filgotinib (Jyseleca®) use in patients with moderately to severely active UC within multiple European registries	*Objective*: To evaluate the effectiveness of the additional RMMs for filgotinib use in patients with UC who initiate treatment with filgotinib in Europe.	Drug utilisation study (DUS) using a non-interventional follow-up cohort design with secondary use of European registries. The study population will include patients with moderate to severe active UC identified from European registries who initiate treatment with filgotinib following approval in Europe, launch/commercial availability for the treatment of UC and implementation of the additional RMMs in each country.	Interim study report (Year 2) Final study report (Year 4)	Q4 2027 Q1 2030

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 46: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit-risk)				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA Ongoing	To evaluate the long-term safety and tolerability of filgotinib for the treatment of RA in subjects who received treatment in the parent studies	Serious and opportunistic infections, Herpes zoster (important identified risk) Malignancy, Venous thromboembolism, GI perforation, MACE, NMSC, Hyperlipidaemia,	Submission of final study report	Q2 2026

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
		Varicella zoster, Fractures (Important potential risks) Use in the very elderly (>75 years) (Missing information)		
GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries Ongoing	To evaluate the incidence rates of infections, malignancy, cardiovascular and other safety events of special interest in RA patients initiating treatment with filgotinib. For context, incidence rates will also be calculated in comparator cohorts depending on data availability.	Serious and opportunistic infections, Herpes zoster (important identified risk) Malignancy, Venous thromboembolism, GI perforation, MACE, NMSC, Hyperlipidaemia, Varicella zoster, Fractures (Important potential risks)	Interim reports Final report	2 yearly Q2 2031
GLPG0634-CL-408 (GS-EU-417-9050, GS-EU-417-9051, GS-EU-417-9052, GS-EU-417-5884, GS-EU-417-5885) Non-interventional, post-authorisation, cohort safety study evaluating the effectiveness of the additional RMMs for filgotinib (Jyseleca®) use in patients with moderate to severe active RA within European registries. Ongoing	To evaluate the effectiveness of the additional RMMs for filgotinib use in RA patients who initiate treatment with filgotinib.	Not applicable	Interim study report (Year 2) Final study report (Year 4)	Q1 2025 Q2 2027
GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with UC	To observe the long-term safety of filgotinib in subjects who have completed or met protocol specified efficacy discontinuation criteria in a prior Gilead-sponsored	Serious and opportunistic infections, Herpes Zoster (Important identified risks) Malignancy, Venous thromboembolism, GI perforation, MACE, NMSC, Hyperlipidaemia, Varicella zoster,	Submission of final study report	Q4 2027

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Ongoing	filgotinib treatment study in UC.	Fractures (Important potential risks)		
GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, Post-authorisation, Prospective Safety Study of Filgotinib in Patients with Moderately to Severely Active UC: a European multi registry-based study Ongoing	To evaluate the incidence rates of serious and opportunistic infections, malignancy, cardiovascular and other safety events of special interest in UC patients initiating treatment with filgotinib. For context incidence rates will also be calculated in comparator cohorts depending on data availability.	Serious and opportunistic infections, Herpes zoster (important identified risk) Malignancy, Venous thromboembolism, GI perforation, MACE, NMSC, Hyperlipidaemia, Varicella zoster, Fractures (Important potential risks)	Interim report Annual progress reports Final report	Approximately 5 years after start of data collection Yearly April 2032, 12 months after the end of data collection in all participating countries
GLPG0634-CL-417 (GS-EU-418-5981) Non-interventional, post-authorisation, prospective cohort study evaluating the effectiveness of the additional RMMs for filgotinib (Jyseleca®) use in patients with moderately to severely active UC within multiple European registries Planned	To evaluate the effectiveness of the additional RMMs for filgotinib use in patients with UC who initiate treatment with filgotinib in Europe	Not applicable	Interim study report (Year 2) Final study report (Year 4)	Q4 2027 Q1 2030

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 47: Planned and Ongoing Post-authorisation Efficacy Studies That are Conditions of the Marketing Authorisation or That are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None.				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1 Routine Risk Minimisation Measures

The routine risk minimisation measures (RMMs) for Jyseleca in the EU comprise of the SmPC, the package leaflet (PL), and the legal status of the product. Jyseleca is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the treatment of RA or UC (SmPC Section 4.2). The routine risk minimisation recommendations provided by the SmPC and PL are described further by safety concern in Table 48. The legal status can be considered a general measure applicable to all individual safety concerns.

Table 48: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
Serious and opportunistic infections	*Routine risk communication:* SmPC Section 4.2, 4.3, 4.4, 4.8 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* PL Section 2 provides guidance for the patient on signs and symptoms of infection and when to contact a healthcare professional. Section 4.3 of the SmPC contraindicates filgotinib in active TB and active serious infections. Recommendation in SmPC Section 4.2 to avoid initiation or interrupt treatment in patients with a serious infection, an absolute lymphocyte count <0.5 x 10^9 cells/L or an absolute neutrophil count <1.0 x 10^9 cells/L. Recommendation in SmPC Section 4.4 on the management of infections in patients receiving filgotinib, and advice on patients at increased risk of infection. Recommendation in SmPC Section 4.4 to screen for TB and to initiate antimycobacterial therapy in patients with latent TB before administering filgotinib, and not to administer filgotinib to patients with active TB. The warning also recommends that patients are monitored for signs and symptoms of TB, including patients who tested negative for latent TB prior to initiating treatment. Section 4.4 also provides advice on the management of viral reactivation, including Herpes zoster and viral hepatitis, as well as advice on use of live vaccines, including prophylactic zoster vaccinations. Recommendation in SmPC Section 4.2 to adjust the dose in patients aged 65 years and older. Recommendation in SmPC Section 4.2 that filgotinib is not recommended in patients with UC aged 75 years and older, as there is no data in this population. Cautionary statement in SmPC Section 4.4 in patients 65 years of age and older that filgotinib should only be used if no suitable treatment alternatives are available.

	Other routine RMMs beyond the Product Information: Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
Herpes zoster	*Routine risk communication:* SmPC Section 4.4, 4.8 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* PL Section 2 provides guidance for the patient on signs and symptoms of herpes zoster and when to contact a healthcare professional. Section 4.4 provides advice on the management of viral reactivation as well as the use of live vaccines, including Herpes zoster. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
Important Potential Risks	
Embryolethality and teratogenicity	*Routine risk communication:* SmPC Section 4.3, 4.6, 5.3 Package leaflet (PL) Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the potential risk:* Filgotinib is contraindicated in pregnancy. Recommendations on contraceptive measures to be taken by women of childbearing potential are included in SmPC Section 4.6, and in the PL Section 2. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
Malignancy	*Routine risk communication:* SmPC Section 4.4 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the potential risk:* Recommendation in SmPC Section 4.2 to adjust the dose in adults at increased risk of malignancy. Cautionary statement in SmPC Section 4.4 indicating that 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. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
Venous thromboembolism (DVT and PE)	*Routine risk communication:* SmPC Section 4.4 PL Section 2

	Routine risk minimisation activities recommending specific clinical measures to address the potential risk: Recommendation in SmPC Section 4.2 to adjust the dose in adults at increased risk of VTE. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
Gastrointestinal (GI) perforation	*Other routine RMMs beyond the Product Information:* Specific adverse reaction follow-up questionnaire Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
Non-melanoma skin cancer (NMSC)	*Routine risk communication:* SmPC Section 4.4 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the potential risk:* Recommendation in SmPC Section 4.2 to adjust the dose in patients with specific risk factors. Recommendation in Section 4.4 for periodic skin examination for patients at risk of skin cancer. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
MACE	*Routine risk communication:* SmPC Section 4.4 *Routine risk minimisation activities recommending specific clinical measures to address the potential risk:* Recommendation in SmPC Section 4.2 to adjust the dose in adults at increased risk of MACE. Cautionary statement in SmPC Section 4.4 indicating that in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, filgotinib should only be used if no suitable treatment alternatives are available. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
Hyperlipidemia	*Routine risk communication:* SmPC Section 4.2, 4.4, 4.8 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the potential risk:* Section 4.2 provides guidance on lipid monitoring and advice on the management of patients with hyperlipidaemia. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.

Varicella zoster	*Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
Fractures	*Routine risk communication:* None *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
Missing Information	
Use in patients with evidence of untreated chronic infection with hepatitis B or C	*Routine risk communication:* SmPC Section 4.4 PL Section 2
Effect on vaccination efficacy	*Routine risk communication:* SmPC Section 4.4 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.4 provides a recommendation that immunisations are updated in agreement with current guidelines before initiating treatment.
Use in the very elderly (>75 years)	*Routine risk communication:* SmPC Section 4.2, 4.4, 4.8 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.2 provides advice that a starting dose of 100 mg q.d. is recommended for patients with RA aged 65 years and above as clinical experience is limited, and that filgotinib is not recommended in patients with UC aged 75 years and older, as there is no data in this population. Section 4.4 advises that as there is a higher incidence of serious infections in the elderly, caution should be used when treating this population. Section 4.8 advises that there was a higher incidence of serious infections in patients with RA 75 years and older, although data are limited.

V.2 Additional Risk Minimisation Measures

V.2.1 Direct Healthcare Professional Communication

As requested during the procedure under Article 20 for Jyseleca (EMEA/H-A20/1517/C/005113/0014), a direct healthcare professional communication (DHPC) is created that will inform prescribers on possible risks associated with the use of JAK inhibitors. The letter informs prescribers on the identified risks related to serious and opportunistic infections, and the potential risks of malignancies, VTE, and MACE. Guidance is also provided on the recommended use of JAK inhibitors in patients with risk factors for these specific safety concerns. The updated recommendations to minimise the risk of malignancy, MACE, serious infections, VTE and mortality with the use of JAK inhibitors will be a joint letter written in

collaboration with all MAHs of JAK inhibitors authorised in the EU for the treatment of inflammatory disorders. This letter will be distributed once at the end of the procedure under Article 20. The measures of effectiveness will be restricted to the process metrics as all MAHs have already dedicated outcome metrics in place to monitor the overall effectiveness of the additional RMMs implemented.

V.2.1 Healthcare Professional Guide

Objectives:

The guide will inform prescribers of the importance of avoiding filgotinib during pregnancy. Guidance is also provided on the use and dosing of filgotinib in patients with risk factors for specific safety concerns. Advice on the management of the following safety concerns is provided:

Important identified risks

- Serious and opportunistic infections
- Herpes Zoster

Important potential risks

- Embryolethality and teratogenicity
- Malignancies (including NMSC)
- Venous thromboembolism
- Major adverse cardiovascular events (MACE)

Missing information

- Use in the very elderly (>75 years)

Rationale for the additional risk minimisation activity:

Considered essential for the safe and effective use of the medicinal product. The HCP guide will provide prescribers with advice according to current data.

Target audience and planned distribution path:

The HCP guide will be provided at an individual Member State level.

Plans to evaluate the effectiveness of the interventions and criteria for success:

A cohort of patients in a disease registry receiving treatment with filgotinib will be observed for the occurrence of events relating to the key risk minimisation messages.

V.2.2 Patient Alert Card

Objectives:

The PAC informs patients of the importance of avoiding filgotinib during pregnancy. The PAC also informs patients of important signs and symptoms of infections and venous thromboembolic events and when to contact their doctor. The PAC advises the patient that their cholesterol will be monitored as this is an important risk factor for CV disease. The PAC provides information on vaccinations that the patient can share with HCPs other than their Rheumatologist.

Rationale for the additional risk minimisation activity:

Considered essential for the safe and effective use of the medicinal product.

Target audience and planned distribution path:

The PAC will be given to the patient by the prescriber. A QR code will also direct the patient to a website.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The additional risk minimisation measures are studied for effectiveness in specific PASS as described in Table 49.

V.3 Summary of Risk Minimisation Measures

Table 49: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Serious and opportunistic infections	*Routine risk communication:* SmPC Section 4.2, 4.3, 4.4, 4.8 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* PL Section 2 provides guidance for the patient on signs and symptoms of infection and when to contact a healthcare professional. Section 4.2 of the SmPC recommends to adjust the dose in patients aged 65 years and older.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Serious and opportunistic infections adverse event follow-up form *Additional pharmacovigilance activities:* RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Section 4.3 of the SmPC contraindicates filgotinib in active TB and active serious infections. Recommendation in SmPC Section 4.2 to avoid initiation or interrupt treatment in patients with a serious infection, an absolute lymphocyte count <0.5 x 109 cells/L or an absolute neutrophil count <1.0 x 109 cells/L. Recommendation in SmPC Section 4.4 on the management of infections in patients receiving filgotinib, and advice on patients at increased risk of infection. Recommendation in SmPC Section 4.4 to screen for tuberculosis (TB) and to initiate antimycobacterial therapy in patients with latent TB before administering filgotinib, and not to administer filgotinib to patients with active TB. The warning also recommends that patients are monitored for signs and symptoms of TB, including patients who tested negative for latent TB prior to initiating treatment. Section 4.4 also provides advice on the management of viral reactivation, including Herpes zoster and viral hepatitis, as well as advice on use of live vaccines, including prophylactic zoster vaccinations. Cautionary statement in SmPC Section 4.4 in patients 65 years of age and older filgotinib should only be used if no suitable treatment alternatives are available. Recommendation in SmPC Section 4.8 that a starting dose of 100 mg is administered to RA patients aged 65 years and older as there was a higher incidence of serious infections in this age group. Filgotinib is not recommended in patients with UC aged 75 years and older, as there is no data in this population. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional RMMs:* HCP guide, PAC, DHPC	to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A Long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Herpes zoster	*Routine risk communication:* SmPC Section 4.4, 4.8 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.4 provides advice on the management of viral reactivation as well as use of live vaccines, including Herpes zoster. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional RMMs:* HCP guide, PAC	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Varicella zoster virus (VZV) infection: Primary varicella (Chicken pox) or Herpes zoster (Shingles) follow-up form *Additional pharmacovigilance activities:* RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional, post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study
Important Potential Risks		
Embryolethality and teratogenicity	*Routine risk communication:* SmPC Section 4.3, 4.6, 5.3 Package leaflet (PL) Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Filgotinib is contraindicated in pregnancy. Recommendations on contraceptive measures to be taken by women of childbearing potential are included in SmPC Section 4.6 and PL Section 2. *Other routine RMMss beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Pregnancy Report Form Pregnancy Outcome Form *Additional pharmacovigilance activities:* None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional RMMs: HCP guide, PAC	
Malignancy	*Routine risk communication:* SmPC Section 4.4 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.2 of the SmPC recommends to adjust the dose in adults at increased risk of malignancy. Cautionary statement in SmPC Section 4.4 indicating that 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. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional RMMs:* HCP guide, PAC, DHPC	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Malignancy adverse event follow-up form *Additional pharmacovigilance activities:* RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional post-authorisation, prospective safety study of filgotinib in the treatment of patients with moderately to severely active UC in Europe
Venous thromboembolism (DVT and PE)	*Routine risk communication:* SmPC Section 4.4 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.2 of the SmPC recommends to adjust the dose in adults at increased risk of VTE. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional RMMs:* HCP guide, PAC, DHPC	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Venous thromboembolism adverse event follow-up form *Additional pharmacovigilance activities:* RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional, post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely Active UC: a European multi registry-based study
Gastrointestinal (GI) perforation	*Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Gastrointestinal perforation adverse event follow-up form *Additional pharmacovigilance activities:* RA: GS-US-417-0304 (Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely Active UC: a European multi registry-based study
Non-melanoma skin cancer (NMSC)	*Routine risk communication:* SmPC Section 4.4 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.2 of the SmPC recommends to adjust the dose in patients with specific risk factors.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Non-Melanoma Skin cancer adverse event follow-up form *Additional pharmacovigilance activities:* RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Recommendation in Section 4.4 for periodic skin examination for patients at risk of skin cancer. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional RMMs:* HCP guide, PAC, DHPC	GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study
MACE	*Routine risk communication:* SmPC Section 4.4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.2 of the SmPC recommends to adjust the dose in adults at increased risk of MACE. Cautionary statement in SmPC Section 4.4 indicating that in patients 65 years of age and older, patients who are current or past long-time smokers, and with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, filgotinib should only be used if no suitable treatment alternatives are available. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional RMMs:* HCP guide, PAC, DHPC	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* MACE adverse event follow-up form *Additional pharmacovigilance activities:* RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study
Hyperlipidemia	*Routine risk communication:* SmPC Section 4.2, 4.4, 4.8 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:*	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Hyperlipidaemia adverse event follow-up form

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Section 4.2 provides guidance on lipid monitoring and advice on the management of patients with hyperlipidaemia. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.	*Additional pharmacovigilance activities:* RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study
Varicella zoster	*Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Varicella zoster virus (VZV) infection: Primary varicella (Chicken pox) or Herpes zoster (Shingles) follow-up form; *Additional pharmacovigilance activities:* RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		patients with moderately to severely active UC: a European multi registry-based study
Fractures	*Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.	*Additional pharmacovigilance activities:* RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study
Missing Information		
Use in patients with evidence of untreated chronic infection with hepatitis B or C	*Routine risk communication:* SmPC Section 4.4 PL Section 2	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Effect on vaccination efficacy	*Routine risk communication:* SmPC Section 4.4 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.4 provides a recommendation that immunisations are updated in agreement with current guidelines before initiating treatment.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Use in the very elderly (>75 years)	*Routine risk communication:* SmPC Section 4.2, 4.4, 4.8	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 provides advice that a starting dose of 100 mg q.d. is recommended for patients with RA aged 65 years and above, and filgotinib is not recommended in patients with UC aged 75 years and older as there is no data in this population. Section 4.4 advises that as there is a higher incidence of serious infections in the elderly, caution should be used when treating this population. Section 4.8 advises that there was a higher incidence of serious infections in patients 65 years and older. *Additional RMMs:* HCP guide	*Additional pharmacovigilance activities:* RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-408 (GS-EU-417-9050, GS-EU-417-9051, GS-EU-417-9052, GS-EU-417-5884, GS-EU-417-5885) Non-interventional, post-authorisation, cohort safety study evaluating the effectiveness of the additional RMMs for filgotinib (Jyseleca®) use in patients with moderate to severe active RA within European registries.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR JYSELECA® (FILGOTINIB)

This is a summary of the risk management plan (RMP) for Jyseleca. The RMP details important risks of Jyseleca, how these risks can be minimised, and how more information will be obtained about Jyseleca's risks and uncertainties (missing information).

Jyseleca's summary of product characteristics (SmPC) and its PL give essential information to healthcare professionals and patients on how Jyseleca should be used.

This summary of the RMP for Jyseleca should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Jyseleca's RMP.

I. The Medicine and What is it Used for

Jyseleca is authorised for monotherapy or in combination with methotrexate for the treatment of adult patients with moderately to severely active RA. Jyseleca is also authorised for the treatment of adult patients with moderately to severely active UC (see SmPC for the full indication). It contains filgotinib as the active substance and it is given orally.

Further information about the evaluation of Jyseleca's benefits can be found in Jyseleca's EPAR, and in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/jyseleca.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Jyseleca, together with measures to minimise such risks and the proposed studies for learning more about Jyseleca's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- specific information, such as warnings, precautions and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- important advice on the medicine's packaging;
- the authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- the medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures (RMMs).

In the case of Jyseleca, these measures are supplemented with additional RMMs mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Jyseleca is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Jyseleca are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Jyseleca. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of Important Risks and Missing Information from Part II: Module SVIII	
Important identified risk	Serious and opportunistic infections
	Herpes zoster
Important potential risk	Embryolethality and teratogenicity
	Malignancy
	Venous thromboembolism (DVT and PE)
	Gastrointestinal (GI) perforation
	Non-melanoma skin cancer (NMSC)
	MACE
	Hyperlipidemia
	Varicella zoster
	Fractures
Missing information	Use in patients with evidence of untreated chronic infection with hepatitis B or C
	Effect on vaccination efficacy
	Use in the very elderly (>75 years)

II.B. Summary of Important Risks

Jyseleca has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy should be initiated by a doctor experienced in the management of RA or UC (as described in Section 4.2 of the SmPC).

Important identified risk: Serious and Opportunistic Infections	
Evidence for linking the risk to the medicine	Serious and opportunistic infections have been reported with the use of other JAK inhibitors and other immunomodulatory drugs used to treat RA or UC, such as tumor necrosis factor (TNF) inhibitors. However, from the pivotal clinical trial data for filgotinib in the Integrated Safety Summary (ISS) for RA, the rate of serious infections is lower than the published rate for biological DMARDs.
Risk factors and risk groups	Patients with RA and patients with UC are at increased risk of developing infections, particularly septic arthritis and pulmonary infections, compared to those without these conditions. The reasons are multifactorial, including a poorly functioning immune system and concomitant use of immunosuppressant medications such as glucocorticoids. Tuberculosis (TB) and other opportunistic infections (OIs) occur more frequently in patients with RA and UC, and this risk is elevated by the use of glucocorticoids and certain biologic therapies. Patients with RA who are elderly, >65 years, on concomitant immunosuppressive therapy, or who have comorbid conditions such as diabetes, may be at increased risk of infection.
Risk minimisation measures	*Routine risk communication:* SmPC Section 4.2, 4.3, 4.4, 4.8 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* PL Section 2 provides guidance for the patient on signs and symptoms of infection and when to contact a healthcare professional. Section 4.3 of the SmPC contraindicates filgotinib in active TB and active serious infections. Recommendation in SmPC Section 4.2 to avoid initiation or interrupt treatment in patients with a serious infection, an absolute lymphocyte count <0.5 x 10^9 cells/L or an absolute neutrophil count <1.0 x 10^9 cells/L. Recommendation in SmPC Section 4.4 on the management of infections in patients receiving filgotinib, and advice on patients at increased risk of infection. Recommendation in SmPC Section 4.2 to adjust the dose in patients aged 65 years and older. Recommendation in SmPC Section 4.4 to screen for TB and to initiate antimycobacterial therapy in patients with latent TB before administering filgotinib, and not to administer filgotinib to patients with active TB. The warning also recommends that patients are monitored for signs and symptoms of TB, including patients who tested negative for latent TB prior to initiating treatment. Section 4.4 also provides advice on the management

	of viral reactivation, including Herpes zoster and viral hepatitis, as well as advice on use of live vaccines, including prophylactic zoster vaccinations. Recommendation in SmPC Section 4.8 that a starting dose of 100 mg is administered to patients with RA aged 65 years and older as there was a higher incidence of serious infections in this age group. Cautionary statement in SmPC Section 4.4 in patients 65 years of age and older filgotinib should only be used if no suitable treatment alternatives are available. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional RMMs:* HCP guide, PAC, DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study See Section II.C.2. of this summary for an overview of the post-authorisation development plan.
Important identified risk: Herpes Zoster	
Evidence for linking the risk to the medicine	Herpes zoster has been reported with the use of other JAK inhibitors and other immunomodulatory drugs used to treat RA or UC, such as TNF inhibitors. However, from the pivotal clinical trial data for filgotinib in the ISS, the rate of herpes zoster is lower than that published for biological and csDMARDs. The RA ISS is based on a pooled dataset of Phase 2b and 3 studies in RA of subjects receiving at least 1 dose of filgotinib 100 mg or 200 mg q.d. to support the marketing authorisation application for RA. As patients with RA and patients with UC are at a higher risk of herpes zoster, compared to age-matched controls, and the use of immunomodulatory therapy are a possible contributing factor, herpes zoster has been classified as an important identified risk warranting further study as specified in the PV plan of this RMP.
Risk factors and risk groups	Patients with RA and patients with UC are at increased risk of developing herpes zoster compared with age-matched healthy adults. The reasons are multifactorial, including a poorly functioning immune system and concomitant use of immunosuppressant medications such as glucocorticoids, increased age and female sex.

Risk minimisation measures	*Routine risk communication:* SmPC Section 4.4, 4.8 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* PL Section 2 provides guidance for the patient on signs and symptoms of herpes zoster and when to contact a healthcare professional. Section 4.4 provides advice on the management of viral reactivation as well as use of live vaccines, including Herpes zoster. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional RMMs:* HCP guide, PAC
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study See Section II.C.2. of this summary for an overview of the post-authorisation development plan.
Important potential risk: Embryolethality and Teratogenicity	
Evidence for linking the risk to the medicine	Non-clinical findings of embryolethality and teratogenicity were observed at exposures slightly higher than the human dose of 200 mg once daily. Embryo-fetal development studies were conducted in rats and rabbits. Visceral and skeletal malformations and/or variations were observed at all dose levels of filgotinib and its active metabolite.
Risk factors and risk groups	Pregnant women and women of childbearing potential.
Risk minimisation measures	*Routine risk communication:* SmPC Section 4.3, 4.6, 5.3 Package leaflet (PL) Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:*

	Filgotinib is contraindicated in pregnancy. Recommendations on contraceptive measures to be taken by women of childbearing potential are included in SmPC Section 4.6 and PL Section 2. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA. *Additional RMMs:* HCP guide, PAC
Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	Patients with RA and patients with UC have an increased risk of some types of malignancy, for example lung, lymphoma, CRC, as well as overall malignancy. It is currently unknown if filgotinib affects this risk. The incidence rate for overall malignancies in filgotinib-treated groups for the clinical trial dataset was lower than for published rates in the RA population and real-world (claims) data for the UC population. The IRs of malignancy events in the UC ISS were low. However, clinical trial data are insufficient to assess the potential incidence of malignancies.
Risk factors and risk groups	Patients with familial history of malignancy or lifestyle risk factors, such as tobacco or alcohol use, obesity. The risk of malignancy increases with age.
Risk minimisation measures	Routine risk communication: SmPC Section 4.4 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Recommendation in SmPC Section 4.2 to adjust the dose in adults at increased risk of malignancy. Cautionary statement in SmPC Section 4.4 indicating that 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. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA. *Additional RMMs:* HCP guide, PAC, DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048 GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries

	UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study See Section II.C.2. of this summary for an overview of the post-authorisation development plan.
Important potential risk: Venous Thromboembolism (DVT and PE)	
Evidence for linking the risk to the medicine	VTEs (DVT and PE) have been observed with filgotinib treatment in patients with RA. However, from the pooled clinical trial data for filgotinib in the indication of RA, no increase in reports of VTEs was seen for filgotinib (100 mg and 200 mg doses) compared to placebo or comparators (MTX, ADA). All patients who developed a VTE had recognised risk factors such as advanced age, immobilisation, obesity, smoking, prior history of deep venous thrombosis (DVT) and pulmonary embolism (PE), heart failure or hormone replacement therapy. Population-based cohort studies suggested an increased risk of VTE in RA patients. An incidence rate (IR) of VTE of 0.61 per 100 person-years in RA patients, which was approximately 2.4 times (95% CI 2.1 – 2.8) higher than the rate in the non-RA population matched for age, sex and index date, was reported in a retrospective US cohort study. A recent epidemiologic analysis based on a US medical claims database indicated an unadjusted VTE IR of 0.58 per PYE (CI 0.59-0.60). The exposure-adjusted incidence rate (IR) (0.2 per 100 PYE, 95% CI 0.1 – 0.4 and 0.0 per 100 PYE, 95% CI 0.0-0.3 for 200 mg q.d. and 100 mg q.d. respectively) of VTEs for filgotinib treatment in the pooled data is within the expected background rate of the target population based on the above literature (0.61 per 100 PYE) and the real-world (claims) data. UC: In the UC program, only 1 filgotinib-treated subject experienced PE, and no filgotinib-treated subjects experienced venous thrombosis (excluding PE).
Risk factors and risk groups	The patients who developed VTEs with filgotinib treatment had at least one of the following recognised risk factors including prior history of VTE, advanced age, hormone replacement treatment, obesity, smoking or immobilisation.
Risk minimisation measures	Routine risk communication: SmPC Section 4.4 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the potential risk:* Recommendation in SmPC Section 4.2 to adjust the dose in adults at increased risk of VTE. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional RMMs:*

	HCP guide, PAC, DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study See Section II.C.2. of this summary for an overview of the post-authorisation development plan.
Important potential risk: Gastrointestinal Perforation	
Evidence for linking the risk to the medicine	GI perforation has been reported with the use of tofacitinib in addition to other immunomodulatory drugs used in the treatment of RA including TNF inhibitors. Although there is a pharmacologically plausible basis for an association between JAK inhibitors and GI perforation, there is insufficient evidence to establish it as an adverse effect of filgotinib treatment at this time. Furthermore, the exposure-adjusted IR (0.1 per 100 PYE, 95% CI 0.0-0.4 and 0.0 per 100 PYE, 95% CI 0.0-0.2 for 200 mg q.d. and 100 mg q.d., respectively) of GI perforation for filgotinib treatment in the pooled data is within the expected background rate of the target population based on real-world (claims) data (0.10, 95% CI 0.10-0.11, per 100 PYE) (Gilead data on file). Patients with RA may be at an increased risk of GI perforation due to prescribed medications (NSAIDs), and/or because of the consequences of the disease process (e.g. vasculitis). In the UC development program, no filgotinib-treated subjects reported a treatment-emergent adverse event of GI perforation.
Risk factors and risk groups	Antecedent diverticulitis, use of glucocorticoids, exposure to NSAIDS, increasing age, and other GI conditions represent risk factors for GI perforation. Advanced age and use of immunosuppressive medications are common in the moderately to severely active RA population, therefore placing this population at greater risk.
Risk minimisation measures	*Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies

	GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study See Section II.C.2. of this summary for an overview of the post-authorisation development plan.
Important potential risk: NMSC	
Evidence for linking the risk to the medicine	NMSC has been reported with filgotinib treatment in patients with RA. From the pooled clinical trial data for filgotinib in the indication of RA, similar incidence of NMSC was noted across filgotinib (including 100 mg and 200 mg doses) and placebo or comparators. Most NMSC events were reported in white elderly (≥65 years old) patients with concomitant medication of MTX. Prior history of NMSC was noted in some patients who developed NMSC during the filgotinib treatment. Epidemiologic studies showed an increased risk of development of NMSC in RA patients, which is in alignment with the result of a meta-analysis showing a RR of 2.02 (95% CI 1.11-3.95) for NMSC in RA patients. Development of NMSC in RA patients was associated with use of prednisone (HR 1.28, p=0.014) alone or with combination MTX and TNF inhibitors (RR 1.97, p=0.001), in addition to established risk factors. A meta-analysis has recently supported the association of increased risk of skin cancers, especially squamous cell cancer (SCC) (RR 1.28, 95% CI 1.19-1.3; RR 1.30, 95% CI 1.09-1.54 respectively) in RA patients with the use of TNF inhibitors compared to RA patients without anti-TNF drugs. The EAIR (0.2 per 100 PYE, 95% CI 0.1-0.4 and 0.1 per 100 PYE, 95% CI 0.0-0.4 for filgotinib 200 mg q.d. and 100 mg q.d., respectively) for NMSC in the pooled filgotinib data was lower than and a real-world (claims) data (0.57 per 100 PYE, 95% CI 0.56-0.58) (Gilead data on file) in the target population of RA patients. UC: NMSC have been reported with filgotinib treatment in patients with UC. All NMSC events were reported in Caucasian subjects, most were elderly (≥65 years old). Prior history of NMSC, and additional risk factors were noted in some patients who reported NMSC during filgotinib treatment. The incidence of NMSC is increased in patients with UC compared to general population. The increased risk for NMSC in UC population might be attributed to the underlying immune dysfunction of UC as well as the use of immunosuppressive medication, in particular thiopurine (Long et al. 2011, 2012; Kappelman et al. 2014; Loo et al. 2019). In the Induction Studies, the EAIRs for NMSC were low: 2 subjects in the filgotinib 200 mg group experienced NMSC (1 subject experience basal cell carcinoma and 1 Bowen's disease) (EAIR = 1.8/100 PYE [95% CI: 0.2, 6.7]), 1 subject in the placebo group experienced basal cell carcinoma (EAIR = 1.7/100 PYE [95% CI: 0.0, 9.4]). In the Maintenance Study, the EAIRs for NMSC were also low: 1 subject who received filgotinib 100 mg experienced basal cell carcinoma (EAIR = 0.8/100 PYE [95% CI: 0.0, 4.6]).

	The expected background rate of NMSC in UC patients based on real-world (claims) data is 0.98 per 100 PYE, 95% CI 0.96-1.01 (Gilead data on file). However, the filgotinib clinical trial data in the RA or the UC populations is considered to be insufficient to assess the potential incidence of NMSC.
Risk factors and risk groups	Advanced age (≥65 years old) and Caucasian race were identified as risk factors in the filgotinib RA clinical program. The risk factors that are generally recognised for NMSC also include sun exposure (i.e. UV), immunosuppressive therapies, phototherapy, ionizing radiation, male sex, and previous history of NMSC.
Risk minimisation measures	Routine risk communication: SmPC Section 4.4 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Recommendation in SmPC Section 4.2 to adjust the dose in patients with specific risk factors as NMSC. Recommendation in Section 4.4 for periodic skin examination for patients at risk of skin cancer. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional RMMs:* HCP guide, PAC, DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries. UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study See Section II.C.2. of this summary for an overview of the post-authorisation development plan.

Important potential risk: MACE	
Evidence for linking the risk to the medicine	Filgotinib treatment was associated with dose-dependent increases in total cholesterol and high-density lipoprotein (HDL) levels, while low density lipoprotein (LDL) levels were slightly increased. LDL/HDL ratios were generally unchanged. Lipid changes were observed within the first 12 weeks of filgotinib treatment and remained stable thereafter. Long-term exposure to increases in blood lipids in the general population would be expected to be associated with adverse cardiovascular (CV) outcomes including major cardiovascular adverse events (MACE), but published data indicate that they may not be harmful to RA patients as the benefits of suppression of inflammation may outweigh the risk of the lipid changes (Myasoedova et al. 2011). UC is associated with an increased risk of coronary artery disease, myocardial infarction, cerebrovascular ischemic events, and mesenteric ischemia compared to those without UC despite the lower prevalence of classical CV risk factors in UC population. The reason is considered to be multifactorial including the inflammatory state associated with the disease and short- and long-term effects of UC therapies. The increased risk may be more pronounced in women compared to men, and in younger patients compared to early patients (Kristensen et al. 2013; Singh et al. 2014; Schicho et al. 2015). Although treatment with filgotinib was associated with increases in total cholesterol, LDL and HDL levels; it is currently unknown if the changes in blood lipids will be associated with adverse CV outcomes for patients with UC with long-term exposure to filgotinib. With RA patients and patients with UC being at a higher risk of CV disease, and the long-term effects of lipid changes on adverse CV outcomes uncertain, MACE has been classified as an important potential risk warranting further study as specified in the PV plan of this RMP.
Risk factors and risk groups	Patients with RA have a substantially elevated risk of cardiovascular morbidity and mortality. CV disease risk in older patients (≥75 years) with RA has been reported to be more than 3-fold the Framingham-predicted risk for the general population, and female patients with RA have demonstrated a 2-fold higher risk of myocardial infarction compare with female patients without RA. The increased risk of CV disease in the RA population cannot be entirely explained by traditional cardiovascular risk factors, thus indicating that RA-specific characteristics, especially systemic inflammation and disease activity, may be associated with increased cardiovascular risk. Traditional CV risk factors such smoking, dyslipidemia, obesity, hypertension, diabetes mellitus, age and prior CV events may also apply to patients with RA. As the number of patients in whom MACE has been identified in clinical trials remains very low, no specific risk factors for MACE have been identified with filgotinib.
Risk minimisation measures	*Routine risk communication:* SmPC Section 4.4

	Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation in SmPC Section 4.2 to adjust the dose in adults at increased risk of MACE. Cautionary statement in SmPC Section 4.4 indicating that in patients 65 years of age and older, patients who are current or past long-time smokers, and with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, filgotinib should only be used if no suitable treatment alternatives are available. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional RMMs:* HCP guide, PAC, DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study See Section II.C.2. of this summary for an overview of the post-authorisation development plan
Important potential risk: Hyperlipidaemia	
Evidence for linking the risk to the medicine	In clinical trials, filgotinib treatment was associated with dose-dependent increases in total cholesterol and high-density lipoprotein (HDL) levels, while low density lipoprotein (LDL) levels were slightly increased. LDL/HDL ratios were generally unchanged. Lipid changes were observed within the first 12 weeks of filgotinib treatment and remained stable thereafter.
Risk factors and risk groups	Modifiable risk factors for hyperlipidemia include a diet high in saturated fats, physical inactivity, smoking and obesity. Other risk factors include biliary obstruction, chronic kidney disease, type 2 diabetes mellitus, high blood pressure, and hypothyroidism. Familial hypercholesterolemia (a monogenic disorder) is estimated to occur in 1:500 individuals in the general population. RA itself is an established risk factor for dyslipidemia.

Risk minimisation measures	Routine risk communication: SmPC Section 4.2, 4.4, 4.8 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.2 provides guidance on lipid monitoring and advice on the management of patients with hyperlipidaemia. *Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries. UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study See Section II.C.2. of this summary for an overview of the post-authorisation development plan.
Important potential risk: Varicella Zoster	
Evidence for linking the risk to the medicine	Primary varicella zoster infection in adults is rare as most people are exposed to the virus in childhood or have been vaccinated. No signal for varicella zoster infection has been detected in the filgotinib RA or UC clinical trial programs. As RA patients with no history of prior infection who are being treated with JAK inhibitors or other immunomodulatory drugs are at a higher risk of complications if a primary infection occurs, varicella zoster has been classified as an important potential risk warranting further study as specified in the PV plan of this RMP.
Risk factors and risk groups	Patients with RA and patients with UC are at increased risk of developing infections, compared to those without these conditions. The reasons are multifactorial, including a poorly functioning immune system and concomitant use of immunosuppressant medications such as glucocorticoids. Adult RA patients may be at risk of complications of primary varicella zoster virus infection, which are most commonly pneumonia.
Risk minimisation measures	*Other routine RMMs beyond the Product Information:*

	Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study See Section II.C.2. of this summary for an overview of the post-authorisation development plan.
Important potential risk: Fractures	
Evidence for linking the risk to the medicine	Various studies have shown that RA is a risk factor for bone fracture in both men and women, with comparable risks of fractures at the vertebral body and hip (Hooyman et al. 1984; Michel et al. 1993; Kröger et al. 1994; West et al. 1994; Lane et al. 1995; Haugeberg et al. 2000; Staa et al. 2006). A review of the literature also suggests that there is an association between IBD and the risk of developing osteoporotic fractures (Staa et al. 2003; Hidalgo et al. 2019).
Risk factors and risk groups	Subjects with RA and UC have a greater risk of fracture compared to the general population. The most marked risk was observed in the RA population, which had the highest incidence and greatest RR compared to the general population among studies reviewed across both diseases, followed by UC.
Risk minimisation measures	*Other routine RMMs beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries UC: GS-US-418-3899 (SELECTION LTE) A long-term extension study to evaluate the safety of filgotinib in subjects with UC

	GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study. See Section II.C.2. of this summary for an overview of the post-authorisation development plan
Missing information: Use in Patients With Evidence of Untreated Chronic Infection With Hepatitis B or C	
Risk minimisation measures	*Routine risk communication:* SmPC Section 4.4 PL Section 2
Missing information: Effect on Vaccination Efficacy	
Risk minimisation measures	*Routine risk communication:* SmPC Section 4.4 PL Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.4 provides a recommendation that immunisations are updated in agreement with current guidelines before initiating treatment.
Missing information: Use in the Very Elderly (>75 Years)	
Risk minimisation measures	*Routine risk communication:* SmPC Section 4.2, 4.4, 4.8 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.2 provides advice that a starting dose of 100 mg q.d. is recommended for patients with RA aged 65 years and above, and filgotinib is not recommended in patients with UC aged 75 years and older, as there is no data in this population. Section 4.4 advises that as there is a higher incidence of serious infections in the elderly, caution should be used when treating this population. Section 4.8 advises that there was a higher incidence of serious infections in patients with RA 65 years and older. *Additional RMMs:* HCP guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RA: GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GLPG0634-CL-408 (GS-EU-417-9050, GS-EU-417-9051, GS-EU-417-9052, GS-EU-417-5884, GS-EU-417-5885) Non-interventional, post-authorisation, cohort safety study evaluating the effectiveness of the additional RMMs for filgotinib (Jyseleca®) use in patients with moderate to severe active RA within European registries. See Section II.C.2. of this summary for an overview of the post-authorisation development plan.

II.C. Post-authorisation Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Jyseleca.

II.C.2. Other Studies in the Post-authorisation Development Plan

Short Study Name	Purpose of the Study
GLPG0634-CL-304 (GS-US-417-0304, Finch 4) long-term extension study in RA	To evaluate the long-term safety and tolerability of filgotinib for the treatment of RA in subjects who received treatment in the parent studies
GLPG0634-CL-403 (GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883) Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA within European registries	To evaluate the incidence rates of infections, malignancy, cardiovascular and other safety events of special interest in RA patients initiating treatment with filgotinib. For context, incidence rates will also be calculated in comparator cohorts depending on data availability.
GLPG0634-CL-408 (GS-EU-417-9050, GS-EU-417-9051, GS-EU-417-9052, GS-EU-417-5884, GS-EU-417-5885) Non-interventional, post-authorisation cohort safety study evaluating the effectiveness of the additional RMMs for filgotinib (Jyseleca®) use in patients with moderate to severe active RA within European registries	To evaluate the effectiveness of the additional RMMs for filgotinib use in RA patients who initiate treatment with filgotinib.
UC: GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with UC	To observe the long-term safety of filgotinib in subjects who have completed or met protocol specified efficacy discontinuation criteria in a prior Gilead-sponsored filgotinib treatment study in UC.
GLPG0634-CL-413 (GS-EU-418-5980) Non-interventional, post-authorisation, prospective safety study of filgotinib in patients with moderately to severely active UC: a European multi registry-based study	To evaluate the incidence rates of serious and opportunistic infections, malignancy, cardiovascular and other safety events of special interest in patients with UC initiating treatment with filgotinib. For context, incidence rates will also be calculated in comparator cohorts depending on data availability.
GLPG0634-CL-417 (GS-EU-418-5981) Non-interventional, post-authorisation, prospective cohort study evaluating the effectiveness of the additional RMMs for filgotinib (Jyseleca®) use in patients with moderately to severely active UC within European registries	To evaluate the effectiveness of the additional RMMs for filgotinib use in patients with UC who initiate treatment with filgotinib in Europe.

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ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

As described in the filgotinib SmPC, Annex II.D, following additional RMMs are proposed:

Prior to launch of Jyseleca in each Member State the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The objective of the programme is to increase awareness of healthcare professionals (HCPs) and patients on the risks of serious and opportunistic infections, foetal malformations (pregnancy risk), venous thromboembolisms (VTEs), and major cardiovascular events (MACE), and malignancies including non-melanoma skin cancer (NMSC) and the management of these risks.

The MAH shall ensure that in each Member State where Jyseleca is marketed, all HCPs and patients/carers who are expected to prescribe, dispense or use Jyseleca have access to/are provided with the following educational package:

The HCP educational material should contain:

- SmPC
- Guide for healthcare professionals
- Patient Alert Card (PAC)

The Guide for healthcare professionals shall contain the following key elements:

- General introductory language that the HCP guide contains important information to assist the discussion with patients when prescribing filgotinib. The guide also informs on steps which can be taken to reduce a patient's risk for key safety aspects of filgotinib.
- Language for HCPs to inform patients of the importance of the PAC
- Risk of serious and opportunistic infections including tuberculosis (TB) and herpes zoster
  - Information on the risk of infections during filgotinib treatment
  - Details on the management of the risk of infection with suggested clinical measures, i.e. what contraindications should be considered prior to initiation of filgotinib, screening for TB, herpes zoster, viral hepatitis and steps to take in the event of an infection
  - Information on avoidance of live, attenuated vaccines immediately prior to or during filgotinib treatment
  - Information on appropriate instructions for patients to seek urgent medical attention should they develop any signs suggestive of an infection
- Risk of embryolethality and teratogenicity
  - Information on the risk of teratogenicity with filgotinib treatment
  - Details on the steps required to minimise the risk of exposure during pregnancy for women of childbearing potential based on the following: filgotinib is contraindicated during pregnancy, women of childbearing potential must be encouraged to use effective

contraception during treatment and for at least 1 week after stopping filgotinib treatment, to advise patients to notify their HCP immediately if they think they could be pregnant or if pregnancy is confirmed, HCPs should actively discuss with patients any current or future pregnancy plans
    - Language to advise patients who are breast-feeding or intend to breast-feed that filgotinib should not be used
- Risk of venous thromboembolism (VTE)
    - Guidance on the use of filgotinib in patients with risk factors for VTE
    - Information on the risk of VTE with filgotinib treatment
    - Details on the management of the risk of VTE with suggested clinical measures, i.e. discontinuation of filgotinib treatment in the event of VTE clinical features occurrence, periodic re-evaluation of patients' risks for VTEs
- Indication and posology statements provided to reinforce in whom filgotinib should be used
- Risk of major adverse cardiovascular events (MACE)
    - Guidance on the use of filgotinib in patients with risk factors for MACE
    - Information on the risk of MACE with filgotinib treatment
    - In patients at high risk for MACE filgotinib should only be used if no suitable treatment alternatives are available, with examples who may be at high risk
    - Information on the risk of an increase in lipid parameters including dose-dependent increases in total cholesterol, and high-density lipoprotein
- Risk of malignancies (including non-melanoma skin cancer [NMSC])
    - In patients at high risk for malignancy filgotinib should only be used if no suitable treatment alternatives are available, with examples who may be at high risk
    - Reminder about the need for periodic skin examination for patients
- Prescribing in the elderly (65 years and above)
    - Information on the treatment patients aged 65 years and above with filgotinib
    - Guidance on the dose of filgotinib to be used in patients with rheumatoid arthritis aged 65 years and above
    - Language to reinforce risks in these patients
- Instructions for how to access digital HCP information
- Instructions on where to report adverse events

The patient information pack should contain:

- Patient information leaflet
- Patient Alert Card (PAC)

The PAC shall contain the following key messages:

- Contact details of the filgotinib prescriber
- Language that the PAC should be carried by the patient at all times and instruction to share it with HCPs involved in their care (i.e. non-filgotinib prescribers, emergency room HCPs, etc.)
- Information on the signs and symptoms of DVT or PE which are essential for the patient to be aware of, so that medical attention can be sought
- Information on the signs and symptoms of serious and opportunistic infections, including herpes zoster, that are essential for the patient to be aware of, so that medical attention can be sought
  - Information to advise patients and their HCPs about the risk of immunisation with live vaccines during filgotinib treatment
- Information on pregnancy, contraception and breast-feeding
  - Clear message that filgotinib must not be used in pregnancy
  - Guidance for patients to use effective contraception while taking filgotinib, and for at least 1 week after stopping filgotinib treatment
  - Advice that filgotinib should not be used while breast-feeding
- Information about monitoring cholesterol levels during treatment.
- Risk of heart disease:
  - Describe signs/symptoms of heart disease that the patient needs to be aware of, so that they can seek attention from their HCP
- Reminder of the risk of cancer. Regarding skin cancer reminder to let their doctor know if they notice any new growth on the skin

Galápagos	Post-Marketing Pregnancy Report Form	
Version #: 1.0	Document #: 25743	Effective Date: 15 Feb 2022

Please complete as many details as possible

1. SOURCE DETAILS		
Type of Report:	☐ Initial ☐ Follow-up	☐ Spontaneous Report
Sender's Case Reference Number: (if applicable)		☐ Non-Interventional Study
Name of Program: (in case of solicited, organized data collection, specify the name)		☐ Market Research Program
Country:		☐ Patient Support Program
Date of this report (dd/mmm/yyyy):		☐ Other (specify):

2. PATIENT INFORMATION					
EXPOSED PARENT'S DETAILS					
Exposed Parent:	☐ Mother ☐ Father	**Initials:**		**Date of Birth:**	
MOTHER'S DETAILS *Regardless of exposed patient please provide mother's details*					
Weight:	☐ kg ☐ lb	**Height:**	☐ cm ☐ inch	**Age at Conception:**	Years
Ethnic Origin:	☐ Asian ☐ Black ☐ Caucasian ☐ Hispanic ☐ Other (specify):				

RISK FACTORS/RELEVANT MEDICAL HISTORY (MOTHER)		
☐ Allergies ☐ Diabetes ☐ Alcohol ☐ Smoking ☐ Drug abuse ☐ Exposed to chemicals or radiation	☐ Genetic disorders (specify, considering family history as well): ☐ Infection (specify):	☐ Congenital abnormalities (specify considering family history as well): ☐ Other (specify with year of diagnosis):

RISK FACTORS/RELEVANT MEDICAL HISTORY (FATHER)		
☐ Allergies ☐ Diabetes ☐ Alcohol ☐ Smoking ☐ Drug abuse ☐ Exposed to chemicals or radiation	☐ Genetic disorders (specify, considering family history as well): ☐ Infection (specify):	☐ Congenital abnormalities (specify considering family history as well): ☐ Other (specify with year of diagnosis):

3. CURRENT PREGNANCY INFORMATION

Last Menstrual Period Date: (dd/mmm/yyyy)		**Conception Date:** (dd/mmm/yyyy)		**Estimated Date of Delivery:** (dd/mmm/yyyy)	
Any contraception used? ☐ No ☐ Yes If yes, specify:					

4. PRODUCT INFORMATION

Maternal exposure: medications taken 4 weeks before conception and/or during pregnancy or breastfeeding
Paternal exposure: medications taken prior conception
* Note: if more information needs to be reported, please print, and use additional pages

Product #	*1*	*2*	*3*	*4*	*5*	*6*
Product Name						
Product Taken By	☐ Mother ☐ Father	☐ Mother ☐ Father	☐ Mother ☐ Father	☐ Mother ☐ Father	☐ Mother ☐ Father	☐ Mother ☐ Father
Indication						
Start Date						
Stop Date						
Dose; Route						
Frequency						
Batch/Lot Number						
Ongoing?	☐ Yes ☐ Stopped ☐ Unknown	☐ Yes ☐ Stopped ☐ Unknown	☐ Yes ☐ Stopped ☐ Unknown	☐ Yes ☐ Stopped ☐ Unknown	☐ Yes ☐ Stopped ☐ Unknown	☐ Yes ☐ Stopped ☐ Unknown

5. PREVIOUS PREGNANCIES

Previous Pregnancies: ☐ No ☐ Yes If yes, specify how many:

Pregnancies	1#	2#	3#	4#	5#	6#
Pregnancy Outcome: A. Therapeutic abortion B. Spontaneous abortion C. Stillbirth D. Ectopic E. Live birth (pre-term) F. Live birth (full-term) G. Unknown	Year: Outcome:	Year: Outcome:	Year: Outcome:	Year: Outcome:	Year: Outcome:	Year: Outcome:
Infant/Fetal Outcome: 1. Unknown 2. Normal 3. Abnormal, specify: 4. Death, specify if intrauterine death, stillbirth, or neonatal death	Year: Outcome:	Year: Outcome:	Year: Outcome:	Year: Outcome:	Year: Outcome:	Year: Outcome:

6. RELEVANT DIAGNOSTIC TESTS

Test	Date of Test	Result	Comment

7. PREGNANCY/BIRTH OUTCOME

Pregnancy interrupted		**Pregnancy not interrupted**	
☐ Spontaneous abortion ☐ Therapeutic abortion ☐ Ectopic ☐ Stillbirth		☐ Live birth ☐ Ongoing	
Date:		**Date:**	
Gestation week:		**Gestation week:**	
Vaginal delivery ☐ Term ☐ Pre-term ☐ Forceps/Vacuum (instrumental)		**Cesarean** ☐ Scheduled ☐ Emergency	
Date:		**Date:**	
Gestation week:		**Gestation week:**	

8. INFANT INFORMATION

Number of infants:		**Gestational age at delivery/abortion:**	Weeks	**Gender:**	☐ Female ☐ Male		
Weight:	☐ kg ☐ lb	**Length:**	☐ cm ☐ inch	**Head circumference:**	☐ cm ☐ inch		
Apgar Scores at:	1 Min: 5 Min: 10 Min:	**Outcome:**	☐ Normal ☐ Abnormal ☐ Death	**Were there any unusual features about the pregnancy and its outcome?**	☐ Yes ☐ No		
If yes, specify:							

ABNORMALITIES (this section is applicable only if birth outcome was abnormal or death)

Any complication during delivery:			
Specify abnormalities:			
Date of death:		**Autopsy performed:**	☐ Yes ☐ No
Autopsy results: (if applicable)			
Cause of death:			

9. REPORTER DETAILS

Reporter's Name: **Address:** **Postal/Zip Code:** **Country:** **E-mail Address:** **Tel.:** **Signature:**	The reporter is a ☐ **Physician (specify specialty):** ☐ **Nurse** ☐ **Pharmacist** ☐ **Non-healthcare Professional** (consumer/ patient/ relative) ☐ **Legal** ☐ **Company Representative**

10. PERMISSION TO CONTACT HEALTHCARE PROFESSIONAL (HCP)

If the reporter is a consumer/patient, permission is given to contact HCP regarding pregnancy/adverse event(s)?	☐ **YES** ☐ **NO**

HCP's Name: **E-mail Address:** **Tel.:**	**Address:** **Postal/Zip Code:** **Country:**

Please be aware that information provided to Galapagos relating to you, may be used to comply with applicable laws and regulations. Galapagos processes your personal data in accordance with applicable data protection laws, such as the European GDPR. For further information about how Galapagos treats your personal data and about your rights, please consult our privacy statement on www.glpg.com/privacy-notice.

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FILGOTINIB TARGETED QUESTIONNAIRE
Serious and Opportunistic Infections

PATIENT INITIALS:	DATE OF BIRTH (DD/MM/YYYY):	CASE NUMBER:
SEX AT BIRTH: ☐ F ☐ M ☐ NOT STATED	**RACE:** ☐ CAUCASIAN ☐ ASIAN ☐ HISPANIC ☐ OF AFRICAN DESCENT ☐ ABORIGINAL/TORRES STRAIT ISLANDER ☐ AMERICAN INDIAN OR ALASKA NATIVE ☐ NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER ☐ OTHER:	**WEIGHT:** _____ ☐ lbs. ☐ Kg **HEIGHT:** _____ ☐ Cm ☐ Inch

1. Start date of filgotinib (DD/MM/YYYY): _____

2. Was filgotinib interrupted due to the infectious event? YES ☐ NO ☐

   If yes, date held (DD/MM/YYYY): _____

3. Was filgotinib discontinued due to the event? YES ☐ NO ☐

   If yes, date discontinued (DD/MM/YYYY): _____

4. Indication for filgotinib treatment: _____

5. Please provide relevant risk factors for infection present over the preceding month (Check YES, NO or UNK (UNKNOWN):

Hematologic malignancy	☐ YES	☐ NO	☐ UNK		Other cancer	☐ YES	☐ NO	☐ UNK
Neutropenia	☐ YES	☐ NO	☐ UNK		Glucocorticoid use	☐ YES	☐ NO	☐ UNK
Other immunosuppressive drug	☐ YES	☐ NO	☐ UNK		Diabetes Mellitus	☐ YES	☐ NO	☐ UNK
Defective cell-mediated immunity	☐ YES	☐ NO	☐ UNK		Organ rejection	☐ YES	☐ NO	☐ UNK
Severe malnutrition	☐ YES	☐ NO	☐ UNK		Pulmonary disease	☐ YES	☐ NO	☐ UNK
Hypogammaglobulinemia	☐ YES	☐ NO	☐ UNK		Asplenia	☐ YES	☐ NO	☐ UNK
Post hematopoietic cell transplant	☐ YES	☐ NO	☐ UNK		Heart disease	☐ YES	☐ NO	☐ UNK
Post solid organ transplant	☐ YES	☐ NO	☐ UNK		Traumatic injury	☐ YES	☐ NO	☐ UNK
Prior antibiotic treatment	☐ YES	☐ NO	☐ UNK		HIV infection	☐ YES	☐ NO	☐ UNK
Other inflammatory diseases	☐ YES	☐ NO	☐ UNK		End stage renal disease	☐ YES	☐ NO	☐ UNK
Primary immunodeficiencies	☐ YES	☐ NO	☐ UNK		Other:			
Please provide details of all risk factors identified above:								

6. Please provide any prior treatment regimens for the filgotinib-treated disease (if applicable):

Start Date (DD/MM/YYYY)	Duration	Regimen

7. Provide any history of other infectious events over the past 6 months:

Date (DD/MM/YYYY)	Details

8. Does the patient have a history of opportunistic infections? YES ☐ NO ☐

   If Yes, please provide details: _____

9. Was the patient treated previously with chemotherapy? YES ☐ NO ☐

   If Yes, please provide details including specific regimen(s) with treatment dates: _____

10. Onset date of symptoms for the current infectious event (DD/MM/YYYY): _____

11. What were the presenting symptoms of this infectious event? _____

12. What was the final diagnosis? _____

13. Please describe the clinical course of this infectious event (e.g., septic shock or organ failure): _____

14. Please provide anatomic location of infection: _____

15. Was causative organism positively identified? YES ☐ NO ☐

    If Yes, please specify organism: _____

    From what specimen type was the organism identified? _____

16. Please provide any additional pathogen characteristics identified (virulence factors or drug resistance):

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17. Was the infection an opportunistic infection? YES ☐ NO ☐ If Yes, please provide:

Additional risk factors for susceptibility to opportunistic infections: _____

Clinical features distinguishing the infection as opportunistic (e.g., extent of involvement, atypical site involvement, etc.): _____

18. Please provide results of relevant diagnostic investigations for this event (e.g., culture, WBC, ANC, etc.):

Date (DD/MM/YYYY)	Test	Results (attach copies of relevant laboratory printouts, if available)

19. Please provide results of relevant pathology, radiographic investigations or imaging studies for this infectious event:

Date (DD/MM/YYYY)	Test	Results (attach copies of relevant laboratory printouts, if available)

20. Please provide medications used for treatment of this reported infectious event:

Drug name	Start Date (DD/MM/YYYY)	Stop Date (DD/MM/YYYY)

21. Level of Care (check all applicable)

Out-patient ☐ Hospitalization ☐ ICU ☐

Supplemental O2 ☐ Mechanical ventilation ☐

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22. Please provide event OUTCOME (check **one,** which is most appropriate)**:**

☐ Continuing/Not Resolved
☐ Improved
☐ Resolved
☐ Resolved with sequelae (specify sequelae/details):_____

Resolution date (DD/MM/YYYY):_____
☐ Unknown/Lost to follow up
☐ Fatal******, **Date of death** (DD/MM/YYYY):_____

** 23. Autopsy performed (if applicable)? ☐ **Yes** ☐ **No** ☐ **UNK**

Cause of death (per autopsy findings):

Additional autopsy findings:

24. Any additional relevant information:

Reporter Signature: _____ Date DD/MM/YYYY: _____

Reporter Name Printed: _____

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FILGOTINIB TARGETED QUESTIONNAIRE
Malignancy

PATIENT INITIALS:	DATE OF BIRTH (DD/MM/YYYY):	CASE NUMBER:
SEX AT BIRTH ☐ F ☐ M ☐ NOT STATED	RACE: ☐ CAUCASIAN ☐ ASIAN ☐ HISPANIC ☐ OF AFRICAN DESCENT ☐ ABORIGINAL/TORRES STRAIT ISLANDER ☐ AMERICAN INDIAN OR ALASKA NATIVE ☐ NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER ☐ OTHER:	WEIGHT: HEIGHT: _____ ☐ lbs _____ ☐ Cm _____ ☐ Kg _____ ☐ Inch

1. Reported Event(s): _____ Event Onset Date DD/MM/YYYY: _____

   ☐ Neoplasm (benign mass/lesions) ☐ Possible malignant tumor - not yet confirmed

   ☐ Neoplasm, malignant

2. **Please specify primary neoplasm site (if relevant): _____**

3. Please provide results of relevant diagnostic investigations for this event:

Date (DD/MM/YYYY)	Test	Results (attach copies of relevant laboratory printouts, if available)
	Histopathology (please indicate stage/grade, staging classification and tissue source)	
	Ultrasound	
	CAT scan	
	MRI	
	Other (e.g., PET scan, endoscopy, etc.)	

4. Medical history/Risk factors for this event:

Cancer	☐ YES	☐ NO		Family history of cancer	☐ YES	☐ NO
Chemotherapy	☐ YES	☐ NO		Radiation therapy	☐ YES	☐ NO
Estrogen use/exposure _____ yrs	☐ YES	☐ NO		Tobacco use _____ pack yrs	☐ YES	☐ NO
Diabetes mellitus	☐ YES	☐ NO		Obesity	☐ YES	☐ NO
Alcohol abuse	☐ YES	☐ NO		Interstitial Lung Disease	☐ YES	☐ NO
Environmental exposures	☐ YES	☐ NO		UV exposure	☐ YES	☐ NO
Immunosuppression	☐ YES	☐ NO		Other _____	☐ YES	☐ NO
(If yes for any of the above, provide details):						

5. Treatment provided for this event (please describe): _____

6. **Filgotinib start date DD/MM/YYYY: _____** Starting dose: _____

   Dose at time of event: _____

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7. Indication (underlying disease) for filgotinib treatment: _____

   Length of time patient has had this underlying disease: _____

8. Filgotinib discontinued? ☐ Yes ☐ No If yes, date discontinued DD/MM/YYYY: _____

9. Concomitant Medications/Substances (please include prescription, OTC and herbal): _____

Specify treatment (please provide name, dose and regimen, if available)	**Start date** (DD/MM/YYYY):	**Stop date** (DD/MM/YYYY):	**Ongoing?**
			☐
			☐
			☐
			☐

10. Prior treatment regimens for the filgotinib-treated underlying disease:

Start Date (DD/MM/YYYY)	**Duration**	**Regimen**

11. Please provide event OUTCOME (check one, which is most appropriate):

☐ Continuing/Not Resolved

☐ Improved

☐ Resolved

☐ Resolved with sequelae (specify sequelae/details):

Resolution date (DD/MM/YYYY):

☐ Unknown/Lost to follow up

☐ Fatal**, Date of death (DD/MM/YYYY):

** 12. Autopsy performed (if applicable)? ☐ Yes ☐ No ☐ UNK

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Cause of death (per autopsy findings):

Additional autopsy findings:

Did the patient have a terminal condition (life expectancy less than 6 months)? ☐ Yes ☐ No

Specify:

13. Any additional relevant information:

Reporter Signature: _____ Date (DD/MM/YYYY): _____

Reporter Name Printed: _____

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FILGOTINIB TARGETED QUESTIONNAIRE
Venous thromboembolism (VTE)

PATIENT INITIALS:	DATE OF BIRTH (DD/MM/YYYY):	CASE NUMBER:	
SEX AT BIRTH: ☐ F ☐ M ☐ NOT STATED	RACE: ☐ CAUCASIAN ☐ ASIAN ☐ HISPANIC ☐ OF AFRICAN DESCENT ☐ ABORIGINAL/TORRES STRAIT ISLANDER ☐ AMERICAN INDIAN OR ALASKA NATIVE ☐ NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER ☐ OTHER:	WEIGHT: _____ ☐ lbs. ☐ Kg	HEIGHT: _____ ☐ Cm ☐ Inch

1. Reported Event(s): _____

2. Event Onset Date (DD/MM/YYYY): _____

3. Clinical Presentation (please describe signs and symptoms):_____

4. Was patient on any VTE prophylaxis at the event onset? ☐ **Yes,** specify:_____ ☐ **No**

5. Hospitalization?

☐ **DUE** to this VTE event
☐ Admitted **PRIOR t**o this event, Reason:_____ Date: _____
☐ **NOT** Hospitalized (Outpatient)

6. Filgotinib administration

Indication (underlying disease): _____	
Start Date (DD/MM/YYYY):_ _____	Starting Dose: _____
Did patient continue the same dose until the event onset? ☐ **Yes** ☐ **No**	
CURRENT Dose: _____	Date of dose change (DD/MM/YYYY): _____
Was Filgotinib discontinued DUE TO this event?	☐ **Yes,** specify stop date (DD/MM/YYYY):_____ ☐ **No**

7. Medical history/Risk factors (check **all** that apply):

Personal history of smoking	☐ YES	☐ NO	☐ UNK	Pack-years: ☐ Current ☐ Former, Year quit:			
Family history of thromboembolic events	☐ YES	☐ NO	☐ UNK	Dyslipidemia	☐ YES	☐ NO	☐ UNK

Personal history of pulmonary embolism (PE), other than current event	☐ YES	☐ NO	☐ UNK	Hypertension	☐ YES	☐ NO	☐ UNK
Personal history of deep vein thrombosis (DVT), other than current event	☐ YES	☐ NO	☐ UNK	Congestive heart failure	☐ YES	☐ NO	☐ UNK
Obesity, BMI:	☐ YES	☐ NO	☐ UNK	Chronic renal disease/Nephrotic syndrome	☐ YES	☐ NO	☐ UNK
Immobility prior to event (prolonged bedrest, sitting, travel)	☐ YES	☐ NO	☐ UNK	Peripheral vascular disease	☐ YES	☐ NO	☐ UNK
Recent pelvic/low extremity fractures	☐ YES	☐ NO	☐ UNK	Chronic venous stasis (e.g., varicose veins)	☐ YES	☐ NO	☐ UNK
Recent pregnancy If yes, date of delivery or termination:	☐ YES	☐ NO	☐ UNK	Superficial vein thrombosis (SVT)	☐ YES	☐ NO	☐ UNK
Recent infection	☐ YES	☐ NO	☐ UNK	Intravenous drug use	☐ YES	☐ NO	☐ UNK
Recent myocardial infarction or stroke	☐ YES	☐ NO	☐ UNK	Recent/current central venous catheter	☐ YES	☐ NO	☐ UNK
Hypercoagulability	☐ YES	☐ NO	☐ UNK	Recent transfusion	☐ YES	☐ NO	☐ UNK
Estrogen replacement therapy	☐ YES	☐ NO	☐ UNK	Oral contraception	☐ YES	☐ NO	☐ UNK
Malignancy/cancer	☐ YES	☐ NO	☐ UNK	(If yes, provide details):			
Recent surgery	☐ YES	☐ NO	☐ UNK	(If yes, provide details):			
Recent trauma or injury	☐ YES	☐ NO	☐ UNK	(If yes, provide details):			
Prior JAK inhibitor	☐ YES	☐ NO	☐ UNK	(If yes, provide details):			
Diabetes mellitus	☐ YES	☐ NO	☐ UNK				
(If yes, provide name(s), duration, date discontinued):							
Please provide details for above conditions or specify other relevant medical history not found above:							

8. Concomitant Medications (check **all** that apply):

☐ Hormonal contraceptives (specify):	☐ Glucocorticoids (specify):
☐ Hormone replacement therapy (specify):	☐ Biologics (specify):
☐ Testosterone	☐ Antidepressants or antipsychotics (specify):
☐ SERMs (specify):	☐ Other (specify):
☐ Heparin (specify):	☐ Other (specify):

9. Please provide results of relevant diagnostic investigations for this event:

Diagnostic Test	Date (DD/MM/ YYYY)	Results (attach copies of relevant laboratory printouts, if available)
Chest CT scan		
CT/MRI		
Ultrasound		
Impedance plethysmography		
Venogram		
Ventilation/perfusion scan		
Angiography		
Viscoelastic tests (TEG, ROTEM)		
Other:		

10. Please provide laboratory test results (complete below and/or attach copies of relevant printouts):

Laboratory Test	Normal Range for Your Institution, Units	Baseline value for Patient Date:	Value at time of event Date:	Follow-up Value(s) Date:
D-dimer				
Platelet count				
INR				
Haemoglobin				
Haematocrit				
Testosterone level				
Factor V Leiden				
Prothrombin G20210A				

MTHFR C677T-A1298C				
Homocysteine level				
Factor VIII				
Factor XI				
Protein S				
Protein C				
Activated Protein C resistance				
Plasminogen activator inhibitor-1 (PAI-1) level				
PAI-1 promoter (4G/5G)				
Anticardiolipin Ab, IgG				
Anticardiolipin Ab, IgM				
Anti-beta2-GP I Ab, IgG				
Anti-beta2-GP I Ab, IgM				
Lupus anticoagulant				
Antithrombin level				
Sedimentation rate				
Other:				
Other:				
Other:				

11. Treatment for the VTE event (check **all** that apply and specify in the table below)**:**

☐ Heparin/LMWH*
☐ Antiplatelet agents*
☐ Oral anticoagulant *
☐ Thrombolytic agent*
☐ Angioplasty
☐ Embolectomy
☐ Vena cava filter
☐ Other (specify):

*** Specify VTE treatment/prophylaxis** (please provide name, dose and regimen, if available)	**Start date (DD/MM/YYYY):**	**Stop date (or Ongoing)**
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐

12. What was the etiology of the VTE event? _____

13. Was the VTE event related to Filgotinib treatment? ☐ **Yes** ☐ **No**

Please provide rationale: _____

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14. Please provide event OUTCOME (choose **one,** which is most appropriate)**:**

☐ Continuing/Not Resolved
☐ Improved
☐ Resolved
☐ Resolved with sequelae (specify sequelae/provide details):_____

Resolution date (DD/MM/YYYY):_____
☐ Unknown/Lost to follow up
☐ Fatal******, **Date of death** (DD/MM/YYYY):_____

** 15. Autopsy performed (if applicable)? ☐ **Yes** ☐ **No** ☐ **Unknown**

Cause of death (per autopsy findings): Additional autopsy findings:

16. Any additional relevant information:

Reporter Signature: _____ Date (DD/MM/YYYY): _____

Reporter Name Printed: _____

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FILGOTINIB TARGETED QUESTIONNAIRE

Gastrointestinal Perforation

PATIENT INITIALS:	DATE OF BIRTH (DD/MM/YYYY):	CASE NUMBER:	
SEX AT BIRTH: ☐ F ☐ M ☐ NOT STATED	RACE: ☐ CAUCASIAN ☐ ASIAN ☐ HISPANIC ☐ OF AFRICAN DESCENT ☐ ABORIGINAL/TORRES STRAIT ISLANDER ☐ AMERICAN INDIAN OR ALASKA NATIVE ☐ NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER ☐ OTHER	WEIGHT: _____ ☐ lbs. ☐ Kg	HEIGHT: _____ ☐ Cm ☐ Inch

1. Indication for Filgotinib: _____

2. Start date of Filgotinib DD/MM/YYYY: _____

3. If Filgotinib interrupted/discontinued (circle one), provide date: _____

4. Date of GI perforation: _____ Site of GI perforation: ☐ UNK

_____

5. Please provide the patient's clinical presentation (check all applicable boxes):

☐ Asymptomatic ☐ Fever ☐ Vomiting/Retching ☐ Diarrhea ☐ Melena ☐ Hematochezia ☐ Abdominal Pain

☐ Other (specify): _____

6. Etiology of GI perforation: _____ ☐ UNK

7. Did the patient have any of the acute events below that may have contributed to the perforation? (check all that apply)

☐ Infection/Sepsis ☐ Penetrating abdominal trauma ☐ Other: _____

8. Relevant Medical History _____

Peptic ulcer disease	☐ YES	☐ NO	☐ UNK	Chronic aspirin use	☐ YES	☐ NO	☐ UNK
Renal impairment	☐ YES	☐ NO	☐ UNK	Chronic NSAID use	☐ YES	☐ NO	☐ UNK
GERD/Esophagitis	☐ YES	☐ NO	☐ UNK	Chronic corticosteroid use	☐ YES	☐ NO	☐ UNK
Hiatal hernia	☐ YES	☐ NO	☐ UNK	Chemotherapy	☐ YES	☐ NO	☐ UNK
Inflammatory bowel disease	☐ YES	☐ NO	☐ UNK	Alcohol overuse	☐ YES	☐ NO	☐ UNK
Infectious colitis including C. diff	☐ YES	☐ NO	☐ UNK	Prior bevacizumab treatment	☐ YES	☐ NO	☐ UNK

Ischemic colitis	☐ YES	☐ NO	☐ UNK	Foreign body ingestion	☐ YES	☐ NO	☐ UNK
				Chronic constipation	☐ YES	☐ NO	☐ UNK
Diverticulitis/osis	☐ YES	☐ NO	☐ UNK	Bowel obstruction	☐ YES	☐ NO	☐ UNK
Malignancy	☐ YES	☐ NO	☐ UNK	If yes, site:			
Recent Surgery	☐ YES	☐ NO	☐ UNK	If yes, specify type and date:			
Recent GI instrumentation (eg. endoscopy, stents, tube insertion)	☐ YES	☐ NO	☐ UNK	If yes, specify procedure and date:			
Other (specify):							

9. Concomitant Medications/Substances (include prescription anticoagulants/antiplatelets, PPIs, H2 blockers, OTC, aspirin/NSAIDs, corticosteroids, herbal medication/supplements…):

Start Date (DD/MM/YYYY)	Drug Name/Other Substance and Dosing Regimen	Stop Date (or Ongoing)
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐

10. Please complete the table with available information regarding evaluation of GI perforation (or attach reports):

	Date(s)	Test/Procedure and Results
Laboratory		
Imaging (X-ray, CT, MRI)		
Surgery/Biopsy		

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Other		

11. Please provide the treatment of the perforation event:

☐ Intravenous fluids

☐ Antibiotics (specify) _____

☐ Surgery (describe) _____

☐ RBC transfusion (units) _____

☐ Other (specify) _____

12. Please provide event OUTCOME (choose one, which is most appropriate):

☐ Continuing

☐ Resolved Resolution date (DD/MM/YYYY): _____

☐ Fatal Date of Death (DD/MM/YYYY): _____

Autopsy performed (if applicable)? ☐ Yes ☐ No ☐ UNK

Cause of death (per autopsy findings):

Additional autopsy findings:

13. Any additional relevant information:

Reporter Name Printed: _____

Reporter Signature: _____ Date DD/MM/YYYY: _____

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FILGOTINIB TARGETED QUESTIONNAIRE
Non-Melanoma Skin Cancer (NMSC)

PATIENT INITIALS: _____	DATE OF BIRTH (DD/MM/YYYY): _____	COUNTRY OF ORIGIN: _____	CASE NUMBER: _____
SEX AT BIRTH: ☐ F ☐ M ☐ NOT STATED	RACE: ☐ CAUCASIAN ☐ ASIAN ☐ HISPANIC ☐ OF AFRICAN DESCENT ☐ ABORIGINAL/TORRES STRAIT ISLANDER ☐ AMERICAN INDIAN OR ALASKA NATIVE ☐ NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER ☐ OTHER:		WEIGHT: _____ ☐ lbs. ☐ Kg HEIGHT: _____ ☐ Cm ☐ Inch

COUNTRY OF RESIDENCE _____

1. Reported NMSC Event(s): _____ Event Onset Date DD/MM/YYYY: _____

2. Please specify NMSC cutaneous site: _____

3. Please provide results of relevant diagnostic investigations for this event:

Date (DD/MM/YYYY)	Test	Results (attach copies of relevant laboratory printouts, if available)
_____	Histopathology (please indicate stage/grade, staging classification and tissue source when applicable)	_____
_____	Other (e.g., CT scan, MRI, PET scan, as applicable)	_____

4. Medical history/Risk factors for this event:

Occupational UV exposure	☐ YES	☐ NO	☐ UNK	Northern European ancestry	☐ YES	☐ NO	☐ UNK
Multiple sunburns during childhood	☐ YES	☐ NO	☐ UNK	Fair skin	☐ YES	☐ NO	☐ UNK
Tanning bed use	☐ YES	☐ NO	☐ UNK	Family history of this NMSC	☐ YES	☐ NO	☐ UNK
Psoralen & UVA light therapy (PUVA)	☐ YES	☐ NO	☐ UNK	Tobacco use _____ pack yrs	☐ YES	☐ NO	☐ UNK
Ionizing radiation	☐ YES	☐ NO	☐ UNK	Past hx NMSC: site _____	☐ YES	☐ NO	☐ UNK
Immunosuppression	☐ YES	☐ NO	☐ UNK				
(If yes, provide details): _____							
Predisposition to phototoxicity	☐ YES	☐ NO	☐ UNK				
(If yes, provide condition, e.g. vitiligo, albinism): _____							
Other (please describe): _____							

5. Treatment provided for this event (please describe): _____

6. **Filgotinib start date DD/MM/YYYY:** _____ Starting dose: _____

   Dose at time of event: _____

7. Indication (underlying disease) for Filgotinib treatment: _____

   Length of time patient has had this underlying disease: _____

8. **Filgotinib discontinued?** ☐ Yes ☐ No If yes, date discontinued DD/MM/YYYY: _____

9. **Concomitant Medications/Substances (please include prescription, OTC and herbal)**

Name (Tradename/generic)	Start Date (DD/MM/YYYY)	Stop date or ongoing (DD/MM/YYYY)	Regimen

10. Prior treatment regimens for the Filgotinib-treated underlying disease

Name (Tradename/generic)	Start Date (DD/MM/YYYY)	Stop date or ongoing (DD/MM/YYYY)	Regimen

11. Please provide event OUTCOME (check **one,** which is most appropriate)**:**

☐ Continuing/Not Resolved
☐ Improved
☐ Resolved
☐ Resolved with sequelae (specify sequelae/details):_____

Resolution date (DD/MM/YYYY):_____
☐ Unknown/Lost to follow up
☐ Fatal**, **Date of death** (DD/MM/YYYY):_____
** 12. Autopsy performed (if applicable)? ☐ **Yes** ☐ **No** ☐ **UNK**

Cause of death (per autopsy findings):

Additional autopsy findings:

13. Any additional relevant information:

Reporter Signature: _____ Date DD/MM/YYYY: _____

Reporter Name Printed: _____

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FILGOTINIB TARGETED QUESTIONNAIRE

Major Adverse Cardiovascular Events (MACE) – Stroke, Myocardial infarction, Cardiovascular death

PATIENT INITIALS:	DATE OF BIRTH (DD/MM/YYYY):	CASE NUMBER:
SEX AT BIRTH: ☐ F ☐ M ☐ NOT STATED	**RACE:** ☐ CAUCASIAN ☐ ASIAN ☐ HISPANIC ☐ OF AFRICAN DESCENT ☐ ABORIGINAL/TORRES STRAIT ISLANDER ☐ AMERICAN INDIAN OR ALASKA NATIVE ☐ NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER ☐ OTHER:	**WEIGHT:** ____ ☐ lbs. ☐ Kg **HEIGHT:** ____ ☐ Cm ☐ Inch

1. Event Onset Date DD/MM/YYYY: _____

2. What was the etiology of the event? _____

3. Was the event related to Filgotinib treatment? ☐ **Yes** ☐ **No**

If yes, please provide rationale: _____

4. Other medical history/potential risk factors for the event (check **all** that apply)

Hypertension	☐ YES	☐ NO	☐ UNK	Atrial fibrillation/flutter	☐ YES	☐ NO	☐ UNK
Obesity: BMI	☐ YES	☐ NO	☐ UNK	CKD (GFR<60 ml/min/m2)	☐ YES	☐ NO	☐ UNK
Diabetes/hyperglycemia	☐ YES	☐ NO	☐ UNK	Congestive heart failure	☐ YES	☐ NO	☐ UNK
Dyslipidemia/hyperlipidemia	☐ YES	☐ NO	☐ UNK	Peripheral vascular disease	☐ YES	☐ NO	☐ UNK
Coronary artery disease	☐ YES	☐ NO	☐ UNK	Carotid artery stenosis	☐ YES	☐ NO	☐ UNK
Tobacco use pack yrs	☐ YES	☐ NO	☐ UNK	Implantable ICD user	☐ YES	☐ NO	☐ UNK
Low physical activity/exercise	☐ YES	☐ NO	☐ UNK	Metabolic syndrome	☐ YES	☐ NO	☐ UNK
History of myocardial infarction	☐ YES	☐ NO	☐ UNK	Rheumatoid arthritis	☐ YES	☐ NO	☐ UNK
History of stroke or TIA	☐ YES	☐ NO	☐ UNK	Inflammatory bowel disease	☐ YES	☐ NO	☐ UNK
History of cerebrovascular disease	☐ YES	☐ NO	☐ UNK	HIV infection	☐ YES	☐ NO	☐ UNK
Cocaine/methamphetamine, etc.	☐ YES	☐ NO	☐ UNK	Other chronic inflammation	☐ YES	☐ NO	☐ UNK
Family history of MI, stroke, and/or other cardiovascular events					☐ YES	☐ NO	☐ UNK
(If yes, provide details):							
Recent cardiovascular surgery/procedures					☐ YES	☐ NO	☐ UNK
(If yes, provide details):							
Prior history of coronary revascularization (eg, PCI, CABG)					☐ YES	☐ NO	☐ UNK
(If yes, provide details):							
History of a cardiac arrhythmia (other than atrial fibrillation)					☐ YES	☐ NO	☐ UNK
(If yes, provide details):							
History of a hypercoagulable condition					☐ YES	☐ NO	☐ UNK
(If yes, provide details):							
Other (please describe):							

5. Filgotinib treatment

Indication (underlying disease):	
Start Date (DD/MM/YYYY):	Starting Dose:
Did patient continue the same dose until the event onset?	☐ **Yes** ☐ **No**
CURRENT Dose:	Date of dose change (DD/MM/YYYY):
Was Filgotinib discontinued DUE TO this event?	☐ **Yes,** specify stop date (DD/MM/YYYY): ☐ **No**

6. Concomitant Medications/Substances (please include prescription, OTC and herbal)

Name (Brand/Generic)	Start Date (DD/MM/YYYY)	Stop Date or Ongoing (DD/MM/YYYY)	Regimen

7. Please provide results of relevant diagnostic investigations for this event (respond to questions and attach copies of relevant laboratory printouts, if available):

ECG STANDARD 12-LEAD Date/Time: _____ ☐ Not performed/Not available

Did the ECG show ischemic changes or acute myocardial infarction? ☐ **Yes** ☐ **No** ☐ **UNK** ☐ **Non Evaluable**

If Yes, check **all** that apply:

☐ ST elevation ☐ ST depression ☐ T-wave inversions ☐ LBBB ☐ Q waves ☐ Loss of R waves

☐ New arrhythmia, Specify: _____

☐ Other, Specify: _____

☐ No new findings

Is an ECG prior to current event available for comparison? ☐ **Yes, Date**: _____ ☐ **No** ☐ **UNK**

Were new Q waves identified? ☐ **Yes** ☐ **No** ☐ **UNK**

Was a new LBBB identified? ☐ **Yes** ☐ **No** ☐ **UNK**

ECHOCARDIOGRAPHY Date/Time: _____ ☐ Not performed/Not available

Is the echocardiogram abnormal? ☐ **Yes** ☐ **Ejection Fraction:** _____% ☐ **No** ☐ **UNK**

If **Yes**, check **all** that apply for the **evidence of**:

☐ Systolic dysfunction ☐ Diastolic dysfunction ☐ Regional wall motion abnormality

☐ Other, specify:

CORONAROGRAPHY Date/Time: _____ ☐ Not performed/Not available

Conclusions:

Was revascularization performed/attempted? ☐ Yes ☐ No ☐ UNK

If **Yes**, specify outcome:

BRAIN IMAGING and ANGIOGRAPHY

Computerized Tomography (CT) scan Date: _____ ☐ Not performed/Not available

Magnetic Resonance Imaging (MRI) Date: _____ ☐ Not performed/Not available

CT or MR Angiogram Date: _____ ☐ Not performed/Not available

Is any brain imaging scan abnormal? ☐ **Yes** ☐ **No** ☐ **UNK**

If **Yes**, check **all** that apply for the **evidence of**:

☐ acute/sub acute event ☐ chronic event

☐ brain hemorrhage: ☐ intraparenchymal ☐ intraventricular ☐ subarachnoid ☐ subdural ☐ epidural

☐ hemorrhagic conversion ☐ infarction ☐ tumor ☐ aneurysm ☐ cerebrovascular malformation

☐ Other, specify:

Other Diagnostic Tests	Date (DD/MM/YYYY)	Results (attach copies of relevant laboratory printouts, if available)
Cardiac CT/MRI		
Stress test (ECG, echo, nuclear, etc.)		
MUGA Scan		
Carotid Duplex Ultrasound		
Transcranial Doppler Ultrasound		
Other:		

8. Please provide laboratory test results (complete below and/or attach copies of relevant printouts):

Laboratory Test Results	Normal Range for Your Institution, Units	Baseline value for Patient Date:	Value at time of event Date:	Follow-up Value(s) Date:
[hs] Troponin I				
[hs] Troponin T				
Creatine Kinase (CK)				
CK-MB				
CK, MB %				

CK, MB activity				
BNP				
Hemoglobin				
Hematocrit				
Platelet count				
INR				
D-dimer				
Creatinine				
Potassium				
Magnesium				
Calcium				
Glucose				
Total cholesterol				
HDL				
LDL				
Triglycerides				
Other:				
Other:				
Other:				

9. Treatment for the event (check **all** that apply and specify in the table below)**:**

☐ Thrombolytic/fibrinolytic agent*
☐ Antianginal (nitrates, β-blockers)*
☐ Antiplatelet agents*
☐ Anticoagulant *
☐ Lipid lowering agents/Statins *
☐ Endovascular thrombectomy
☐ Percutaneous coronary intervention
☐ CABG
☐ Carotid endarterectomy/angioplasty/stenting
☐ Other (specify)

*** Specify treatment** (please provide name, dose and regimen, if available)	**Start date** (DD/MM/YYYY):	**Stop date** (DD/MM/YYYY):	**Ongoing?**
			☐
			☐
			☐
			☐

10. Please provide event OUTCOME (check **one,** which is most appropriate)**:**

☐ Continuing/Not Resolved
☐ Improved
☐ Resolved
☐ Resolved with sequelae (specify sequelae/details):_____

Resolution date (DD/MM/YYYY):_____
☐ Unknown/Lost to follow up
☐ Fatal******, **Date of death** (DD/MM/YYYY):_____

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** 11. Autopsy performed (if applicable)? ☐ **Yes** ☐ **No** ☐ **UNK**

Cause of death (per autopsy findings):

Additional autopsy findings:

Did the patient have a terminal condition (life expectancy less than 6 months)? ☐ **Yes** ☐ **No**
Specify:

12. Any additional relevant information:

Reporter Signature: _____ Date (DD/MM/YYYY): _____

Reporter Name Printed: _____

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FILGOTINIB TARGETED QUESTIONNAIRE
Dyslipidemia

PATIENT INITIALS:	DATE OF BIRTH (DD/MM/YYYY):	CASE NUMBER:
SEX AT BIRTH: ☐ F ☐ M ☐ NOT STATED	**RACE:** ☐ CAUCASIAN ☐ ASIAN ☐ HISPANIC ☐ OF AFRICAN DESCENT ☐ ABORIGINAL/TORRES STRAIT ISLANDER ☐ AMERICAN INDIAN OR ALASKA NATIVE ☐ NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER ☐ OTHER:	**WEIGHT:** ____ ☐ lbs. ☐ Kg **HEIGHT:** ____ ☐ Cm ☐ Inch

1. Filgotinib start date (DD/MM/YYYY): _____ Starting dose: _____

2. Was Filgotinib stopped? ☐ Yes ☐ No If yes, stop date: _____

If applicable, describe any change in Filgotinib dose (include date): _____

3. Indication (underlying disease) for Filgotinib treatment: _____

4. Length of time patient has had this underlying disease: _____

5. Has the patient taken lipid-lowering drugs at any time, including before, during or after Filgotinib treatment?
☐ Yes (Complete table below) ☐ No ☐ Unknown

Drug name: _____	Dose: _____	Start date (DD/MM/YYYY) _____	Stop date: _____ -or- ☐ Ongoing
Drug name: _____	Dose: _____	Start date (DD/MM/YYYY) _____	Stop date: _____ -or- ☐ Ongoing
Drug name: _____	Dose: _____	Start date (DD/MM/YYYY) _____	Stop date: _____ -or- ☐ Ongoing

6. Provide lab data relevant to the event

DATE (DD/MM/YYYY)	**TOTAL CHOLESTEROL**	**LDL**	**HDL**	**TRIGLYCERIDES**	**FASTING?**
PRIOR TO INITIATING FILGOTINIB					
					☐ YES ☐ NO ☐ UNK
					☐ YES ☐ NO ☐ UNK
					☐ YES ☐ NO ☐ UNK
AT THE TIME OF THE REPORTED EVENT, AND SUBSEQUENTLY					
					☐ YES ☐ NO ☐ UNK
					☐ YES ☐ NO ☐ UNK
					☐ YES ☐ NO ☐ UNK

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7. Provide relevant medical history/risk factors. Check all that apply.

How much does patient currently smoke tobacco (including e-cigarettes)?	☐ ≥40 cigarettes (≥2 Packs) day	☐ 20-39 cigarettes/day	During past 12 months, how often did patient have a drink containing **alcohol?**	☐ Daily	☐1-2x /week	☐ None
	☐ 10-19 cigarettes/day	☐ <10 cigarettes/day		☐3-4x /week	☐2-3x /month	☐UNK
	☐ None	☐UNK		☐5-6x /week	☐<2-3x /month	
What is patient's lifetime exposure to tobacco	☐ >25 Pack-years	☐ 16-25 pack-years	Family history hyperlipidemia or inherited disorder of lipid metabolism	☐ YES	☐ NO	☐ UNK
	☐ 5-15 pack-years	☐ <5 pack-years				
	☐ None	☐UNK				
Diabetes mellitus	☐ YES	☐ NO	☐UNK	Sedentary lifestyle	☐ YES	☐ NO	☐ UNK
Hypertension	☐ YES	☐ NO	☐UNK	HIV/AIDS	☐ YES	☐ NO	☐ UNK
Hyperlipidemia	☐ YES	☐ NO	☐UNK	Chronic kidney disease	☐ YES	☐ NO	☐ UNK
Nephrotic syndrome	☐ YES	☐ NO	☐UNK	Liver disease	☐ YES	☐ NO	☐ UNK
Hypothyroidism	☐ YES	☐ NO	☐UNK	Obesity	☐ YES	☐ NO	☐ UNK
Atherosclerotic cardiovascular disease (CAD, CVA, PAD, etc)	☐ YES	☐ NO	☐UNK				

Please provide details for above conditions or specify other relevant medical history not found above:

8. Concomitant medications/substances not already specified in Item 5 above. Include prescription, OTC and herbal. Also, include drugs used to treat the underlying condition for which Filgotinib was prescribed.

Start Date (DD/MM/YYYY)	Drug/Other substance	Stop Date or Ongoing (DD/MM/YYYY)
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐

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Reporter Signature: _____ Date DD/MM/YYYY: _____

Reporter Name Printed: _____

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FILGOTINIB TARGETED QUESTIONNAIRE

Varicella zoster virus (VZV) infection: Primary Varicella (Chicken pox) or Herpes zoster (Shingles)

PATIENT INITIALS:	DATE OF BIRTH (DD/MM/YYYY):	CASE NUMBER:	
SEX AT BIRTH: ☐ F ☐ M ☐ NOT STATED	RACE: ☐ CAUCASIAN ☐ ASIAN ☐ HISPANIC ☐ OF AFRICAN DESCENT ☐ ABORIGINAL/TORRES STRAIT ISLANDER ☐ AMERICAN INDIAN OR ALASKA NATIVE ☐ NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER ☐ OTHER:	WEIGHT: _____ ☐ lbs. ☐ Kg	HEIGHT: _____ ☐ Cm ☐ Inch

1. Filgotinib start date (DD/MM/YYYY): _____ Starting dose: _____

2. Disease for which filgotinib was prescribed: _____

3. Length of time patient has had this disease: _____

4. Filgotinib dose at the time the VZV event occurred: _____

5. Action taken with filgotinib due to the event:

   ☐ Filgotinib was stopped Stop date (DD/MM/YYYY): _____
   ☐ Filgotinib was continued / dose was unchanged
   ☐ Filgotinib dose was reduced Date of dose reduction (DD/MM/YYYY): _____ New dose: _____

6. What is the diagnosis for the varicella zoster virus (VZV) event? Select one: ☐ Primary varicella (chicken pox) ☐ Herpes zoster (shingles)

7. Onset date of signs/symptoms of the current VZV event (DD/MM/YYYY): _____

8. What were the presenting signs/symptoms? Include anatomic locations affected (for example, single dermatome, 2 adjacent dermatomes, disseminated cutaneous, visceral organ(s)).

9. Describe the clinical course of this event. Include treatment for the event, outcome information, and whether there were any complications (for example, post-herpetic neuralgic, herpes ophthalmicus, Ramsay Hunt):

10. Was the diagnosis confirmed by lab testing, such as polymerase chain reaction (PCR) or culture? ☐ Yes ☐ No ☐ Unknown

If yes, specify test and result:

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11. Specify all concomitant medications (not already reported). Be sure to include all immunosuppressive or immunomodulatory medications, such as glucocorticoids, disease modifying anti-rheumatic drugs (DMARDs), tumor necrosis factor (TNF)- alpha inhibitors and other biologic therapies.

Concomitant medications (Name and dosing regimen)	**Start date** (DD/MM/YYYY):	**Stop date (or Ongoing)** (DD/MM/YYYY):
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐
		-Or- ☐

12. Has the patient ever been vaccinated against Varicella (chicken pox)? ☐ Yes ☐ No ☐ Unknown
    If yes, date(s) of vaccination (DD/MM/YYYY):

13. Has the patient ever been vaccinated against Herpes zoster (shingles)? ☐ Yes ☐ No ☐ Unknown
    If yes, which vaccine was administered: ☐ Zostavax ☐ Shingrix ☐ Unknown
    Date(s) of administration (DD/MM/YYYY):

14. Has the patient had Varicella (chicken pox) in the past? ☐ Yes ☐ No ☐ Unknown
    If yes, date (DD/MM/YYYY) (or patient's age at the time of infection):

15. Has the patient had Varicella titers checked? ☐ Yes ☐ No ☐ Unknown
    If yes, results of lab test and date:

16. Has the patient ever had Herpes zoster in the past? ☐ Yes ☐ No ☐ Unknown.
    If yes, complete this table:

Date (DD/MM/YYYY)	**Description of Herpes zoster episode(s).** Include whether single dermatome, two adjacent dermatomes, disseminated cutaneous, or if there was visceral organ involvement (specify organ). Also, note any complications.

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17. Medical history/ Risk factors (check all that apply):

Hematologic malignancy	☐ YES	☐ NO	☐ UNK	Other cancer	☐ YES	☐ NO	☐ UNK
Neutropenia	☐ YES	☐ NO	☐ UNK	Diabetes mellitus	☐ YES	☐ NO	☐ UNK
Defective cell-mediated immunity	☐ YES	☐ NO	☐ UNK	Lymphopenia	☐ YES	☐ NO	☐ UNK
Severe malnutrition	☐ YES	☐ NO	☐ UNK	Chronic pulmonary disease	☐ YES	☐ NO	☐ UNK
Hypogammaglobulinemia	☐ YES	☐ NO	☐ UNK	Asplenia	☐ YES	☐ NO	☐ UNK
Post hematopoietic cell transplant	☐ YES	☐ NO	☐ UNK	Chronic kidney disease	☐ YES	☐ NO	☐ UNK
Post solid organ transplant	☐ YES	☐ NO	☐ UNK	HIV infection/ AIDS (CD4:)	☐ YES	☐ NO	☐ UNK
Cirrhosis	☐ YES	☐ NO	☐ UNK	Other:			

Please provide details for above conditions or specify other relevant medical history not found above. For lab data, please include baseline (pre-filgotinib) values and dates.

18. Please provide event OUTCOME (check **one,** which is most appropriate)**:**

☐ Continuing/Not Resolved
☐ Improved
☐ Resolved
☐ Resolved with sequelae (specify sequelae/details):_____

Resolution date (DD/MM/YYYY):_____
☐ Unknown/Lost to follow up
☐ Fatal******, **Date of death** (DD/MM/YYYY):_____

** 19. Autopsy performed (if applicable)? ☐ **Yes** ☐ **No** ☐ **UNK**

Cause of death (per autopsy findings):

Additional autopsy findings:

20. Any additional relevant information:

Reporter Signature: _____ Date (DD/MM/YYYY): _____

Reporter Name Printed: _____