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 package leaflet 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 rheumatoid arthritis (RA). Jyseleca is also authorised for the treatment of adult patients with moderately to severely active ulcerative colitis (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 package leaflet 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 (deep venous thrombosis and pulmonary embolism)
	Gastrointestinal (GI) perforation
	Non-melanoma skin cancer (NMSC)
	MACE
	Hyperlipidemia
	Varicella zoster
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 Janus kinase (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 $<0.5 \times 10^9$ cells/L or an absolute neutrophil count $<1.0 \times 10^9$ 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-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies 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 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-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies 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 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, colorectal cancer, 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-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies 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 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 (Deep Venous Thrombosis and Pulmonary Embolism)	
Evidence for linking the risk to the medicine	VTEs (deep venous thrombosis and pulmonary embolism) 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-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies 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 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-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies 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 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: Non-melanoma Skin Cancer	
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 (Kappelman et al., 2014; Millie D. Long et al., 2011, 2012; 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-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies 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 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; Schicho et al., 2015; S. Singh et al., 2014). 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-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies 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 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-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies 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 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-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies 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 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-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies 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. 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-205 (DARWIN 3) 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-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 Ulcerative Colitis	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 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, cohort, safety study evaluating the effectiveness of the additional RMMs for filgotinib (Jyseleca®) use in patients with	To evaluate the effectiveness of the additional RMMs for filgotinib use in patients with UC who initiate treatment with filgotinib in Europe.

Short Study Name	Purpose of the Study
moderately to severely active UC within European registries	