ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Jyseleca 100 mg film-coated tablets
Jyseleca 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Jyseleca 100 mg film-coated tablets

Each film-coated tablet contains filgotinib maleate equivalent to 100 mg of filgotinib.

Excipient with known effect
Each 100 mg film-coated tablet contains 76 mg of lactose (as monohydrate).

Jyseleca 200 mg film-coated tablets

Each film-coated tablet contains filgotinib maleate equivalent to 200 mg of filgotinib.

Excipient with known effect
Each 200 mg film-coated tablet contains 152 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Jyseleca 100 mg film-coated tablets

Beige 12 × 7 mm, capsule-shaped, film-coated tablet debossed with “G” on one side and “100” on the other side.

Jyseleca 200 mg film-coated tablets

Beige 17 × 8 mm, capsule-shaped, film-coated tablet debossed with “G” on one side and “200” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Jyseleca is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic 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 who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.

4.2 Posology and method of administration

Treatment with filgotinib should be initiated by a physician experienced in the treatment of rheumatoid arthritis or ulcerative colitis.

Posology

Rheumatoid arthritis
The recommended dose of filgotinib for adult patients is 200 mg once daily.
In adults at increased risk of VTE, MACE and malignancy (see section 4.4), 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.

Ulcerative colitis
Induction treatment
The recommended dose for induction treatment is 200 mg once daily.

For patients with ulcerative colitis 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). 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), 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.

Laboratory monitoring, and dose initiation or interruption
Guidance for laboratory monitoring, and dose initiation or interruption is provided in Table 1.
Treatment should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.4).

Table 1: Laboratory measures and monitoring guidance

Laboratory measure	Action	Monitoring guidance
Absolute neutrophil count (ANC)	Treatment should not be initiated, or should be interrupted, if ANC is < 1×10^9 cells/L. Treatment may be restarted once ANC returns above this value	Before treatment initiation and thereafter according to routine patient management
Absolute lymphocyte count (ALC)	Treatment should not be initiated, or should be interrupted, if ALC is < 0.5×10^9 cells/L. Treatment may be restarted once ALC returns above this value	
Haemoglobin (Hb)	Treatment should not be initiated, or should be interrupted, if Hb is < 8 g/dL. Treatment may be restarted once Hb returns above this value	
Lipid parameters	Patients should be managed according to international clinical guidelines for hyperlipidaemia	12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia

Special populations

Elderly

Rheumatoid arthritis

In patients with rheumatoid arthritis 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). For long term treatment, the lowest effective dose should be used.

Ulcerative colitis

In patients with ulcerative colitis aged 65 years of age and older, the recommended dose is 200 mg once daily for the induction treatment and 100 mg once daily for maintenance treatment (see section 4.4). 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 aged 75 years and older as there is no data in this population.

Renal impairment

No dose adjustment is required in patients with mild renal impairment (creatinine clearance [CrCl] ≥ 60 mL/min). A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (CrCl 15 to < 60 mL/min). Filgotinib has not been studied in patients with end stage renal disease (CrCl < 15 mL/min) and is therefore not recommended for use in these patients (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh A or B). Filgotinib has not been studied in patients with severe hepatic impairment (Child-Pugh C) and is therefore not recommended for use in these patients (see section 5.2).

Paediatric population

The safety and efficacy of filgotinib in children under the age of 18 years have not yet been established. No data are available.

Method of administration

Oral use.
Jyseleca can be taken with or without food (see section 5.2). It has not been studied if tablets can be split, crushed, or chewed, and it is recommended that tablets are swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active tuberculosis (TB) or active serious infections (see section 4.4).

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Filgotinib should only be used if no suitable treatment alternatives are available in patients:
-65 years of age and older;
-patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers);
-patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

Immunosuppressive medicinal products

Combination of filgotinib with other potent immunosuppressants such as ciclosporin, tacrolimus, biologics or other Janus kinase (JAK) inhibitors is not recommended as a risk of additive immunosuppression cannot be excluded.

Infections

Infections, including serious infections, have been reported in patients receiving filgotinib. The most frequent serious infection reported with filgotinib was pneumonia (see section 4.8). Among opportunistic infections, TB, oesophageal candidiasis, and cryptococcosis were reported with filgotinib.

The risks and benefits of treatment should be considered prior to initiating filgotinib in patients:
- with chronic or recurrent infection
- who have been exposed to TB
- with a history of a serious or an opportunistic infection
- who have resided or travelled in areas of endemic TB or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infections during and after filgotinib treatment. If an infection develops during treatment with filgotinib, the patient should be carefully monitored and filgotinib treatment should be temporarily interrupted if the patient is not responding to standard antimicrobial therapy. Filgotinib treatment may be resumed once the infection is controlled.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients 65 years of age and older, filgotinib should only be used if no suitable treatment alternatives are available (see section 4.2).

Tuberculosis
Patients should be screened for TB before initiating filgotinib. Filgotinib should not be administered to patients with active TB (see section 4.3). In patients with latent TB, standard antimycobacterial therapy should be initiated before administering filgotinib.

Patients should be monitored for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating treatment.

Viral reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies (see section 4.8). In rheumatoid arthritis clinical studies, the risk of herpes zoster appeared to be higher in female patients, Asian patients, patients ≥ 50 years of age, patients with a medical history of herpes zoster, patients with a medical history of chronic lung disease and patients treated with filgotinib 200 mg once daily. If a patient develops herpes zoster, filgotinib treatment should be temporarily interrupted until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during treatment with filgotinib. Patients who were positive for both hepatitis C antibody and hepatitis C virus RNA were excluded from clinical studies. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical studies.

Malignancy

Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including filgotinib. In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and non-melanoma skin cancer (NMSC) was observed with tofacitinib compared to TNF inhibitors.

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.

Non-melanoma skin cancer
NMSCs have been reported in patients treated with filgotinib. Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer.

Haematological abnormalities

ANC < 1×10^9 cells/L (see section 4.8) and ALC < 0.5×10^9 cells/L were reported in ≤ 1% of patients in the rheumatoid arthritis clinical studies and in < 3% of patients in the ulcerative colitis clinical studies. Treatment should not be initiated, or should be temporarily interrupted, in patients with an ANC < 1×10^9 cells/L, ALC < 0.5×10^9 cells/L or haemoglobin < 8 g/dL observed during routine patient management (see section 4.2).

Vaccinations

Use of live vaccines during, or immediately prior to, filgotinib treatment is not recommended. It is recommended that immunisations, including prophylactic zoster vaccinations, be updated in agreement with current immunisation guidelines prior to initiating filgotinib treatment.

Lipids

Treatment with filgotinib was associated with dose-dependent increases in lipid parameters, including total cholesterol, and high-density lipoprotein (HDL) levels, while low-density lipoprotein (LDL) levels were slightly increased (see section 4.8). LDL cholesterol returned to pre-treatment levels in the majority of patients who started statin therapy while taking filgotinib. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined (see section 4.2 for monitoring guidance).

Major adverse cardiovascular events (MACE)
Events of MACE have been observed in patients taking filgotinib.
In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke, was observed with tofacitinib compared to TNF inhibitors.

Therefore, in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, filgotinib should only be used if no suitable treatment alternatives are available.

Venous thromboembolism (VTE)

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including filgotinib.

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a dose dependent higher rate of VTE including deep venous thrombosis (DVT) and pulmonary embolism (PE) was observed with tofacitinib compared to TNF inhibitors.

In patients with cardiovascular or malignancy risk factors (see also section 4.4 “Major adverse cardiovascular events (MACE)” and “Malignancy”) filgotinib should only be used if no suitable treatment alternatives are available.

In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, filgotinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder.

Patients should be re-evaluated periodically during filgotinib treatment to assess for changes in VTE risk.

Promptly evaluate patients with signs and symptoms of VTE and discontinue filgotinib in patients with suspected VTE, regardless of dose.

Use in patients 65 years of age and older

Considering the increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomised study of tofacitinib (another JAK inhibitor), filgotinib should only be used in these patients if no suitable treatment alternatives are available.

Lactose content

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on filgotinib

Filgotinib is primarily metabolised by carboxylesterase 2 (CES2), which can be inhibited *in vitro* by medicinal products such as fenofibrate, carvedilol, diltiazem or simvastatin. The clinical relevance of this interaction is unknown.

Effect of filgotinib on other medicinal products

Filgotinib is not a clinically relevant inhibitor or inducer of most enzymes or transporters commonly involved in interactions such as cytochrome P450 (CYP) enzymes and UDP-glucuronosyltransferases (UGT).

In vitro studies are inconclusive regarding the potential of filgotinib to induce CYP2B6. *In vivo* induction cannot be excluded.

In vitro studies are inconclusive regarding the potential of filgotinib to induce or inhibit CYP1A2. No clinical studies have been performed to investigate interactions with CYP1A2 substrates and therefore the potential *in vivo* effect of concomitant induction and inhibition of CYP1A2 by filgotinib is unknown. Caution is recommended when filgotinib is co-administered with CYP1A2 substrates with a narrow therapeutic index.

In a clinical pharmacology study, there was no effect on the pharmacokinetics of the combined contraceptive ethinyl estradiol and levonorgestrel when co-administered with filgotinib; thus no dose adjustment of oral contraceptives is required.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception

Women of childbearing potential have to use effective contraception during and for at least 1 week after cessation of filgotinib treatment.

Pregnancy

There are no or limited amount of data from the use of filgotinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Based on findings in animals, filgotinib may cause foetal harm and is therefore contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is unknown whether filgotinib is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded. Therefore, Jyseleca should not be used during breast-feeding.

Fertility

In animal studies, decreased fertility, impaired spermatogenesis, and histopathological effects on male reproductive organs were observed (see section 5.3). The data from two dedicated Phase 2 clinical

studies (MANTA and MANTA RAy, n=240) to evaluate the human testicular safety in men with inflammatory arthritis diseases and inflammatory bowel diseases did not reveal a difference between treatment groups in the proportion of patients who had a 50% or more decrease from baseline in semen parameters at week 13 (pooled primary endpoint: filgotinib 6.7%, placebo 8.3%) and at week 26. Further, the data did not show any relevant changes in sex hormone levels or change from baseline in semen parameters across treatment groups. Overall, these clinical data were not suggestive of filgotinib-related effects on testicular function.

Animal studies did not indicate effects with respect to fertility in females.

4.7 Effects on ability to drive and use machines

Filgotinib has no or negligible influence on the ability to drive and use machines. However, patients should be advised that dizziness has been reported during treatment with Jyseleca (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Rheumatoid arthritis
The most frequently reported adverse reactions are nausea (3.5%), upper respiratory tract infection (URTI, 3.3%), urinary tract infection (UTI, 1.7%), dizziness (1.2%) and lymphopenia (1.0%).

Ulcerative colitis
In general, the overall safety profile observed in filgotinib-treated patients with ulcerative colitis was generally consistent with the safety profile observed in patients with rheumatoid arthritis.

Tabulated list of adverse reactions

The following adverse reactions are based on clinical studies (Table 2). The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1 000 to < 1/100).

Table 2: Adverse reactions

Frequency [a]	Adverse reaction
Infections and infestations	
Common	Urinary tract infection (UTI) Upper respiratory tract infection (URTI)
Uncommon	Herpes zoster Pneumonia Sepsis
Blood and lymphatic system disorders	
Common	Lymphopenia
Uncommon	Neutropenia
Metabolism and nutrition disorders	
Uncommon	Hypercholesterolaemia
Nervous system disorders	
Common	Dizziness
Gastrointestinal disorders	
Common	Nausea
Investigations	
Uncommon	Blood creatine phosphokinase increased

a Frequency based on placebo-controlled pre-rescue period (week 12) pooled across FINCH 1 and 2, and DARWIN 1 and 2, for patients with rheumatoid arthritis who received filgotinib 200 mg. Frequencies reported in the SELECTION study in patients with ulcerative colitis who received filgotinib 200 mg were generally consistent with those reported in the rheumatoid arthritis studies.

Laboratory changes

Creatinine
An increase in serum creatinine occurred with filgotinib treatment. At week 24 in the Phase 3 studies (FINCH 1, 2, and 3), the mean (SD) increase from baseline in serum creatinine was 0.07 (0.12) and 0.04 (0.11) mg/dL for filgotinib 200 mg and 100 mg, respectively. Mean creatinine values remained within the normal range.

Lipids
Treatment with filgotinib was associated with dose-dependent increases in total cholesterol and HDL levels, while 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.

Serum phosphate
Generally mild, transient or intermittent, and dose-dependent decreases in serum phosphate levels occurred during treatment with filgotinib and resolved without discontinuation of treatment. At week 24 in the Phase 3 studies (FINCH 1, 2, and 3), serum phosphate values of less than 2.2 mg/dL (the lower limit of normal) were reported in 5.3% and 3.8% of subjects receiving filgotinib 200 mg and 100 mg, respectively; no values below 1.0 mg/dL were reported.

In placebo-controlled Phase 3 studies with background DMARDs (FINCH 1 and FINCH 2) through 12 weeks, serum phosphate levels of less than 2.2 mg/dL were reported in 1.6%, 3.1%, and 2.4% in the placebo, filgotinib 200 mg, and filgotinib 100 mg groups, respectively.

Description of selected adverse reactions

Infections
Rheumatoid arthritis
In placebo-controlled studies with background DMARDs (FINCH 1, FINCH 2, DARWIN 1, and DARWIN 2), the frequency of infection over 12 weeks in the filgotinib 200 mg group was 18.1% compared to 13.3% in the placebo group. In the MTX-controlled study FINCH 3, the frequency of infection over 24 weeks in the filgotinib 200 mg monotherapy and filgotinib 200 mg plus MTX groups was 25.2% and 23.1%, respectively, compared to 24.5% in the MTX group. The overall exposure-adjusted incidence rate (EAIR) of infections for the filgotinib 200 mg group across all seven Phase 2 and 3 clinical studies (2,267 patients) was 26.5 per 100 patient-years of exposure (PYE).

In placebo-controlled studies with background DMARDs, the frequency of serious infection over 12 weeks in the filgotinib 200 mg group was 1.0% compared to 0.6% in the placebo group. In the MTX-controlled study FINCH 3, the frequency of serious infection over 24 weeks in the filgotinib 200 mg monotherapy and filgotinib 200 mg plus MTX groups was 1.4% and 1.0%, respectively, compared to 1.0% in the MTX group. The overall EAIR of serious infections for the filgotinib 200 mg group across all seven Phase 2 and 3 clinical studies (2,267 patients) was 1.7 per 100 PYE. The most common serious infection was pneumonia. The EAIR of serious infections remained stable with long-term exposure.

In rheumatoid arthritis clinical studies, there was a higher incidence of serious infections in patients aged 65 years and older.

In placebo-controlled studies with background DMARDs, the frequencies of infectious ADRs over 12 weeks for filgotinib 200 mg compared to placebo were: URTI (3.3% *versus* 1.8%), UTI (1.7% *versus* 0.9%), pneumonia (0.6% *versus* 0.4%), and herpes zoster (0.1% *versus* 0.3%). Most of the herpes zoster events involved a single dermatome and were non-serious. The overall EAIR of herpes zoster across all seven Phase 2 and 3 clinical studies (2 267 and 1 647 total patients for 200 mg and 100 mg, respectively) was 1.6 and 1.1 per 100 PYE in the 200 mg group and 100 mg group, respectively.

Ulcerative colitis
The types of serious infections in the ulcerative colitis clinical studies were generally similar to those reported in the rheumatoid arthritis clinical studies with filgotinib monotherapy treatment groups.

Across the two placebo-controlled induction studies, the frequency of serious infections was 0.6% in the filgotinib 200 mg group, 1.1% in the filgotinib 100 mg group, and 1.1% in the placebo group. In the placebo-controlled maintenance study, the frequency of serious infections in the filgotinib 200 mg group was 1%, compared to 0% in the respective placebo group. In the maintenance study filgotinib 100 mg group, the frequency of serious infections was 1.7%, compared with 2.2% in the respective placebo group.

Opportunistic infections (excluding TB)
In rheumatoid arthritis placebo-controlled studies with background DMARDs, there were no opportunistic infections over 12 weeks in the filgotinib 200 mg group or the placebo group. In the MTX-controlled study FINCH 3, the frequency of opportunistic infections over 24 weeks was 0, 0.2%, and 0 in the filgotinib 200 mg monotherapy, filgotinib 200 mg plus MTX, and MTX groups, respectively. The overall EAIR of opportunistic infections for the filgotinib 200 mg group across all seven Phase 2 and 3 rheumatoid arthritis clinical studies (2 267 patients) was 0.1 per 100 PYE.

Nausea
Nausea was generally transient and reported during the first 24 weeks of filgotinib treatment.

Creatine phosphokinase
Dose-dependent increases in creatine phosphokinase (CPK) occurred within the first 12 weeks of filgotinib treatment and remained stable thereafter. At week 24 in the Phase 3 studies (FINCH 1, 2, and 3), the mean (SD) increase from baseline in CPK was -16 (449), 61 (260), and 33 (80) U/L for placebo, filgotinib 200 mg and 100 mg, respectively.

In placebo-controlled Phase 3 studies with background DMARDs (FINCH 1 and FINCH 2) through 12 weeks, CPK elevations > 5 × upper limit of normal (ULN) were reported in 0.5%, 0.3%, and 0.3% of patients in the placebo, filgotinib 200 mg, and filgotinib 100 mg groups, respectively. Most elevations > 5 × ULN did not require treatment discontinuation.

Experience from long-term extension studies

Rheumatoid arthritis
In the long-term extension study DARWIN 3, among patients enrolled from DARWIN 1 (N = 497), 238 patients received filgotinib 200 mg once a day for a median duration of 4.4 years; among patients enrolled from DARWIN 2 (N = 242), 234 patients received filgotinib 200 mg once a day for a median duration of 4.4 years. In the long-term extension study FINCH 4, 1,530 patients received filgotinib 200 mg once daily and 1,199 patients received filgotinib 100 mg once daily for a median duration of 1.5 years. The safety profile of filgotinib was similar to that in the Phase 2 and Phase 3 studies.

Ulcerative colitis
In the long-term extension study (SELECTION LTE) in patients who participated in the SELECTION study, patients received filgotinib 200 mg (N = 871), filgotinib 100 mg (N = 157), or placebo (N = 133) for median durations of 55, 36, and 32 weeks, respectively. The safety profile of filgotinib was similar to that in the SELECTION induction and maintenance studies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Filgotinib has been administered in clinical studies following single and once daily administration up to 450 mg without dose-limiting toxicity. Adverse reactions were comparable to those seen at lower doses and no specific toxicities were identified. Pharmacokinetic data following a single dose of 100 mg filgotinib in healthy subjects indicate that approximately 50% of the administered dose is eliminated within 24 hours of dosing and 90% of the dose is eliminated within 72 hours. In case of an overdose, it is recommended that a patient be monitored for signs and symptoms of adverse reactions. Treatment of overdose with filgotinib consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. It is unknown whether filgotinib can be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA45

Mechanism of action

Filgotinib is an adenosine triphosphate (ATP)-competitive and reversible inhibitor of the JAK family. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane. JAK1 is important in mediating inflammatory cytokine signals, JAK2 in mediating myelopoiesis and erythropoiesis and JAK3 plays critical roles in immune homeostasis and lymphopoiesis. Within the signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity including gene expression. Filgotinib modulates these signalling pathways by preventing the phosphorylation and activation of STATs. In biochemical assays, filgotinib preferentially inhibited the activity of JAK1 and showed > 5-fold higher potency of filgotinib for JAK1 over JAK2, JAK3 and TYK2. In human cellular assays, filgotinib preferentially inhibited JAK1/JAK3-mediated signalling downstream of the heterodimeric cytokine receptors for interleukin (IL)-2, IL-4 and IL-15, JAK1/2-mediated IL-6, and JAK1/TYK2-mediated type I interferons, with functional selectivity over cytokine receptors that signal via pairs of JAK2 or JAK2/TYK2. GS-829845, the primary metabolite of filgotinib, was approximately 10-fold less active than filgotinib in *in vitro* assays, while exhibiting a similar JAK1 preferential inhibitory activity. In an *in vivo* rat model, the overall pharmacodynamic effect was predominantly driven by the metabolite.

Pharmacodynamic effects

Inhibition of IL-6 induced STAT1 phosphorylation
Filgotinib administration resulted in a dose-dependent inhibition of IL-6 induced STAT1 phosphorylation in whole blood from healthy subjects. Filgotinib administration did not affect JAK2-associated GM-CSF induced STAT5 phosphorylation.

Immunoglobulins
In FINCH 1, 2, and 3, the median and interquartile ranges for serum IgG, IgM, and IgA values remained largely within the normal reference ranges through 24 weeks of treatment with filgotinib in patients with rheumatoid arthritis and through 58 weeks of treatment in patients with ulcerative colitis.

Haematologic effects
In FINCH 1, 2, and 3 in patients with rheumatoid arthritis, treatment with filgotinib was associated with a small, transient increase in mean ALC that remained within normal reference ranges and gradually returned to at or near baseline levels with continued treatment by week 12. In FINCH 1, 2, and 3, median haemoglobin values remained stable within the normal range through 24 weeks of

filgotinib treatment. A slight decrease in median platelet counts occurred within the first 4 weeks of filgotinib treatment and remained stable thereafter through 24 weeks. Median platelet counts remained within the normal range.

In SELECTION, in patients with ulcerative colitis, median haemoglobin values remained stable through 58 weeks of filgotinib treatment.

C-reactive protein
Decreases in serum C-reactive protein (CRP) were observed as early as 2 weeks after starting treatment with filgotinib and were maintained through 24 weeks of treatment in patients with rheumatoid arthritis and through 58 weeks of treatment in patients with ulcerative colitis.

Clinical efficacy and safety

Rheumatoid arthritis
The efficacy and safety of filgotinib once daily were assessed in three Phase 3 studies (FINCH 1, 2, and 3). These were randomised, double-blind, multicentre studies in patients with moderate to severe active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria.

FINCH 1 was a 52-week study in 1 755 patients with rheumatoid arthritis who had an inadequate response to MTX. Patients received filgotinib 200 mg once daily, filgotinib 100 mg once daily, adalimumab every 2 weeks, or placebo, all added to stable background MTX. At week 24, patients receiving placebo were re-randomised to filgotinib 100 mg or 200 mg once daily through week 52. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12.

FINCH 2 was a 24-week study in 448 patients with rheumatoid arthritis who had an inadequate response to bDMARDs. Patients received filgotinib 200 mg once daily, filgotinib 100 mg once daily, or placebo, all with a continued stable background dose of conventional synthetic DMARD(s) (csDMARD[s]: MTX, hydroxychloroquine, sulfasalazine, or leflunomide). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12.

FINCH 3 was a 52-week study in 1 249 patients with rheumatoid arthritis who were naïve to MTX therapy. Patients received filgotinib 200 mg once daily plus MTX once weekly, filgotinib 100 mg once daily plus MTX once weekly, filgotinib 200 mg (monotherapy) once daily, or MTX (monotherapy) once weekly. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Clinical response
Higher response rates *versus* placebo or MTX were seen at week 2 for ACR20, and responses were maintained through week 52.

Treatment with filgotinib 200 mg resulted in improvements in all individual ACR components, including tender and swollen joint counts, patient and physician global assessments, Health Assessment Questionnaire Disability Index (HAQ-DI), pain assessment and high sensitivity CRP, compared to placebo or MTX. In two of the Phase 3 studies (FINCH 1 and FINCH 2), the comparison (*versus* placebo) was carried out on top of MTX or csDMARD(s) (see above).

Low disease activity and remission
Across the Phase 3 studies, a significantly higher proportion of patients treated with filgotinib 200 mg plus MTX or other csDMARD achieved low disease activity and/or remission (DAS28-CRP $\leq$ 3.2 and DAS28-CRP < 2.6) at weeks 12 and 24 as compared to placebo or MTX. Filgotinib 200 mg was non-inferior to adalimumab at week 12 for DAS28-CRP $\leq$ 3.2 in FINCH 1 (Table 3).

Table 3: Clinical response at weeks 12, 24 and 52 in FINCH 1, 2, and 3

	FINCH 1 MTX-IR				FINCH 2 bDMARD-IR			FINCH 3 MTX-naïve			
Treatment	**FIL 200 mg**	**FIL 100 mg**	**ADA**	**PBO**	**FIL 200 mg**	**FIL 100 mg**	**PBO**	**FIL 200 mg + MTX**	**FIL 100 mg + MTX**	**FIL 200 mg mono**	**MTX**
	+ MTX				**+ csDMARD**						
N	475	480	325	475	147	153	148	416	207	210	416
Week											
ACR20 (percent of patients)											
12	77***¶	70***	71	50	66***	58***	31	77†††	72††	71††	59
24	78†††	78†††	74	59	69†††	55†††	34	81***	80*	78	71
52	78	76	74	-	-	-	-	75†††	73††	75†††	62
ACR50 (percent of patients)											
12	47†††¶¶¶	36†††	35	20	43†††	32†††	15	53†††	44†††	46†††	28
24	58†††	53†††	52	33	46†††	35††	19	62†††	57††	58††	46
52	62	59	59	-	-	-	-	62†††	59††	61†††	48
ACR70 (percent of patients)											
12	26†††¶¶¶	19†††	14	7	22†††	14†	7	33†††	27†††	29†††	13
24	36†††¶	30†††	30	15	32†††	20††	8	44†††	40†††	40†††	26
52	44	38	39	-	-	-	-	48†††	40††	45†††	30
DAS28-CRP ≤ 3.2 (percent of patients)											
12	50$^{***###}$	39***	43	23	41***	37***	16	56†††	50†††	48†††	29
24	61†††§§§¶¶	53†††§§§	50	34	48†††	38†††	21	69†††	63†††	60†††	46
52	66¶	59	59	-	-	-	-	69†††	60††	66†††	48
DAS28-CRP < 2.6 (percent of patients)											
12	34†††§§§¶¶¶	24†††§§	24	9	22†††	25†††	8	40†††	32†††	30†††	17
24	48***§§§¶¶¶	35***§§§	36	16	31†††	26††	12	54***	43***	42†††	29
52	54¶	43	46	-	-	-	-	53†††	43††	46†††	31
CDAI, change from baseline (mean)											
12	-26.0†††	-23.3†††	-23.5	-20.3	-26.2†††	-23.8†††	-17.3	-27.8†††	-26.1†††	-27.5†††	-22.7
24	-30.6†††	-28.6†††	-28.4	-26.3	-30.9†††	-27.8††	-25.4	-31.3†††	-30.0†††	-31.3†††	-28.2
52	-32.9	-30.9	-31.6	-	-	-	-	-33.8†††	-31.9†	-33.6†††	-31.2

ADA: adalimumab; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying anti-rheumatic drug; FIL: filgotinib; IR: inadequate responder; mono: monotherapy; MTX: methotrexate; PBO: placebo.

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ *versus* placebo (*versus* MTX for FINCH 3) (statistically significant difference with multiplicity adjustment).

† $p \leq 0.05$; †† $p \leq 0.01$; ††† $p \leq 0.001$ *versus* placebo (*versus* MTX for FINCH 3) (nominal p-value).

\# $p \leq 0.05$; ## $p \leq 0.01$; ### $p \leq 0.001$ *versus* adalimumab for FINCH 1 (non-inferiority test, statistically significant difference with multiplicity adjustment) (analysed for DAS28-CRP ≤ 3.2 and < 2.6 pairwise comparisons only).

§ $p \leq 0.05$; §§ $p \leq 0.01$; §§§ $p \leq 0.001$ *versus* adalimumab for FINCH 1 (non-inferiority test, nominal p-value) (analysed for DAS28-CRP ≤ 3.2 and < 2.6 pairwise comparisons only).

¶ $p \leq 0.05$; ¶¶ $p \leq 0.01$; ¶¶¶ $p \leq 0.001$ *versus* adalimumab for FINCH 1 (superiority test, nominal p-value) (analysed for ACR20/50/70, and DAS28-CRP ≤ 3.2 and < 2.6 pairwise comparisons only).

Note: Comparisons were carried out on top of a stable background of MTX (FINCH 1) or csDMARD(s) (FINCH 2).

Radiographic response

Inhibition of progression of structural joint damage was assessed using the modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score, at weeks 24 and 52 in FINCH 1 and FINCH 3.

In patients who had an inadequate response to MTX, treatment with filgotinib plus MTX resulted in statistically significant inhibition of progression of structural joint damage compared to placebo plus MTX at week 24 (Table 4). Analyses of erosion and joint space narrowing scores were consistent with the overall scores.

Table 4: Radiographic response at weeks 24 and 52 in FINCH 1 and 3

	FINCH 1 MTX-IR				FINCH 3 MTX-naïve			
Treatment	**FIL 200 mg**	**FIL 100 mg**	**ADA**	**PBO**	**FIL 200 mg + MTX**	**FIL 100 mg + MTX**	**FIL 200 mg mono**	**MTX**
	+ MTX							
N	475	480	325	475	416	207	210	416
Week								
Modified Total Sharp Score (mTSS), mean (SD) change from baseline								
24	0.13 (0.94)***	0.17 (0.91)***	0.16 (0.95)	0.37 (1.42)	0.21 (1.68)	0.22 (1.53)	-0.04 (1.71)††	0.51 (2.89)
52	0.21 (1.43)	0.50 (2.10)	0.58 (3.62)	-	0.31 (1.81)†††	0.23 (1.11)††	0.33 (1.90)††	0.81 (3.09)
Proportion of patients with no radiographic progression [a]								
24	88%**	86%	86%	81%	81%†	77%	83%†	72%
52	88%	81%	82%	-	81%††	76%	77%	71%

ADA: adalimumab; FIL: filgotinib; IR: inadequate responder; mono: monotherapy; MTX: methotrexate; PBO: placebo.
a No progression defined as mTSS change ≤ 0.
* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 *versus* placebo (statistically significant difference with multiplicity adjustment).
† p ≤ 0.05; †† p ≤ 0.01; ††† p ≤ 0.001 *versus* placebo (*versus* MTX for FINCH 3) (nominal p-value).

Physical function response and health related outcomes
Treatment with filgotinib 200 mg resulted in a significant improvement in physical function, as measured by change from baseline in HAQ-DI (Table 5).

Table 5: Mean change from baseline in HAQ-DI at weeks 12, 24 and 52 in FINCH 1, 2, and 3

	Mean change from baseline										
	FINCH 1 MTX-IR				FINCH 2 bDMARD-IR			FINCH 3 MTX-naïve			
Treatment	**FIL 200 mg**	**FIL 100 mg**	**ADA**	**PBO**	**FIL 200 mg**	**FIL 100 mg**	**PBO**	**FIL 200 mg + MTX**	**FIL 100 mg + MTX**	**FIL 200 mg mono**	**MTX**
	+ MTX				+ csDMARD						
N	475	480	325	475	147	153	148	416	207	210	416
Week											
Health Assessment Questionnaire Disability Index (HAQ-DI)											
Baseline score	1.59	1.55	1.59	1.63	1.70	1.64	1.65	1.52	1.56	1.56	1.60
12	-0.69***	-0.56***	-0.61	-0.42	-0.55***	-0.48***	-0.23	-0.85†††	-0.77†††	-0.76†††	-0.61
24	-0.82†††	-0.75†††	-0.78	-0.62	-0.75†††	-0.60††	-0.42	-0.94***	-0.90**	-0.89†	-0.79
52	-0.93	-0.85	-0.85	-	-	-	-	-1.00†††	-0.97	-0.95†	-0.88

ADA: adalimumab; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; FIL: filgotinib; IR: inadequate responder; mono: monotherapy; MTX: methotrexate; PBO: placebo.
* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 *versus* placebo (statistically significant difference with multiplicity adjustment).
† p ≤ 0.05; †† p ≤ 0.01; ††† p ≤ 0.001 *versus* placebo (*versus* MTX for FINCH 3) (nominal p-value).

Health status outcomes were assessed by the Short Form health survey (SF-36). Patients treated with filgotinib 200 mg plus MTX or other csDMARD demonstrated numerically greater improvement from baseline in the physical component summary score of SF-36 as well as in the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) at weeks 12 and 24 compared to placebo plus MTX/csDMARD or MTX.

Long-term efficacy
In a long-term Phase 2 open-label extension study (DARWIN 3), continued and durable responses were observed, with ACR20/50/70 responses maintained for up to 3 years in patients who received filgotinib 200 mg as monotherapy or with MTX.

Ulcerative colitis

The efficacy and safety of filgotinib once daily were evaluated in a randomised, double-blind, placebo-controlled combined Phase 2b/3 study (SELECTION) in patients with moderately to severely active ulcerative colitis (Mayo Clinic Score 6 to 12; endoscopy subscore ≥ 2; rectal bleeding subscore ≥ 1; stool frequency subscore ≥ 1; and Physician's Global Assessment subscore ≥ 2). SELECTION included two induction studies (UC-1 and UC-2) followed by a maintenance study (UC-3), with a total duration of 58 weeks of therapy. Patients were permitted to use stable doses of concomitant therapies for ulcerative colitis, including oral aminosalicylates, oral corticosteroids (prednisone equivalent dose up to 30 mg/day), and immunomodulators (azathioprine, 6-MP, or methotrexate).

UC-1 was an 11-week induction study in 659 patients with ulcerative colitis who were naïve to biologic therapy and had an inadequate response, loss of response, or intolerance to corticosteroids or immunomodulators. Patients received filgotinib 200 mg once daily (N = 245), filgotinib 100 mg once daily (N = 277), or placebo (N = 137). At baseline, 56% of patients had an endoscopic subscore of 3; 24% were receiving oral corticosteroids only, 23% immunomodulators only, 7% corticosteroids and immunomodulators, and 47% neither corticosteroids nor immunomodulators.

UC-2 was an 11-week induction study in 689 patients with ulcerative colitis who were biologic-experienced and had an inadequate response, loss of response, or intolerance to a tumour necrosis factor (TNF) blocker or vedolizumab. Patients received filgotinib 200 mg once daily (N = 262), filgotinib 100 mg once daily (N = 285), or placebo (N = 142). At baseline, 78% of patients had an endoscopic subscore of 3; 85% had failed at least 1 prior TNF blocker, 52% had failed vedolizumab, and 43% had failed at least 1 TNF blocker and vedolizumab; 36% were receiving oral corticosteroids only, 13% immunomodulators only, 10% corticosteroids and immunomodulators, and 41% neither corticosteroids nor immunomodulators.

The primary endpoint for UC-1 and UC-2 was the proportion of patients who achieved clinical remission at week 10. Clinical remission was defined as MCS endoscopy subscore of 0 or 1 (endoscopy subscore of 0 defined as normal or inactive disease and subscore of 1 defined as presence of erythema, decreased vascular pattern, and no friability), rectal bleeding subscore of 0 (no rectal bleeding), and at least a one point decrease in stool frequency subscore from baseline to achieve 0 or 1. Key secondary efficacy endpoints included MCS remission, endoscopic remission, and histologic remission at week 10.

UC-3 was a 47-week maintenance study in 558 patients with ulcerative colitis who achieved clinical response or remission at week 10 from filgotinib in UC-1 (N = 320) or UC-2 (N = 238). Clinical response was defined as a decrease in MCS of ≥ 3 points and ≥ 30% decrease from baseline, with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1. Patients were re-randomised at week 11 to receive their induction dose of filgotinib or placebo through week 58. As in UC-1 and UC-2, patients were permitted to use stable doses of oral aminosalicylates or immunomodulators; however, corticosteroid tapering was required three weeks after entering this study. The primary endpoint was the proportion of patients who achieved clinical remission at week 58. Key secondary efficacy endpoints were MCS remission, sustained clinical remission, 6-month corticosteroid-free clinical remission, endoscopic remission, and histologic remission at week 58.

Clinical outcomes

Across the UC-1 and UC-2 studies, a significantly greater proportion of patients receiving filgotinib 200 mg achieved clinical remission at week 10 as compared to placebo (Table 6). A significantly greater proportion of biologic-naïve patients (UC-1) receiving filgotinib 200 mg achieved MCS remission, endoscopic remission, and histologic remission at week 10 as compared to placebo (Table 6).

Efficacy in the filgotinib 100 mg group as compared to placebo was not statistically significant at week 10 in either UC-1 or UC-2.

Table 6: Proportion of patients meeting efficacy endpoints at week 10 in induction studies UC-1 and UC-2

Endpoint n (%)	UC-1 Biologic naïve N = 659			UC-2 Biologic experienced [a] N = 689		
	FIL 200 mg N = 245	Placebo N = 137	Treatment difference and 95% CI	FIL 200 mg N = 262	Placebo N = 142	Treatment difference and 95% CI
Clinical remission [b]	64 (26.1%)	21 (15.3%)	10.8% (2.1%, 19.5%) p = 0.0157	30 (11.5%)	6 (4.2%)	7.2% (1.6%, 12.8%) p = 0.0103
Failure to both TNF and vedolizumab [c]	-	-	-	8/120 (6.7%)	1/64 (1.6%)	-
MCS remission [d]	60 (24.5%)	17 (12.4%)	12.1% (3.8%, 20.4%) p = 0.0053	25 (9.5%)	6 (4.2%)	5.3% (−0.1%, 10.7%)
Endoscopic remission [e]	30 (12.2%)	5 (3.6%)	8.6% (2.9%, 14.3%) p = 0.0047	9 (3.4%)	3 (2.1%)	1.3% (−2.5%, 5.1%)
Histologic remission [f]	86 (35.1%)	22 (16.1%)	19.0% (9.9%, 28.2%) p < 0.0001	52 (19.8%)	12 (8.5%)	11.4% (4.2%, 18.6%)

CI: Confidence interval; FIL: filgotinib; MCS: Mayo Clinic Score.

a Biologic experienced = Patients who previously demonstrated an inadequate response, loss of response to, or intolerance of a TNF blocker or vedolizumab.

b Primary endpoint. Clinical remission was defined as MCS endoscopy subscore of 0 or 1 (endoscopy subscore of 0 defined as normal or inactive disease and subscore of 1 defined as presence of erythema, decreased vascular pattern, and no friability), rectal bleeding subscore of 0 (no rectal bleeding), and at least a one point decrease in stool frequency subscore from baseline to achieve 0 or 1.

c Subgroup analysis based on patients with prior treatment failure to both a TNF blocker and vedolizumab.

d MCS remission was defined as MCS ≤ 2 with no individual subscore of > 1.

e Endoscopic remission was defined as MCS endoscopic subscore of 0.

f Histologic remission was assessed using Geboes histologic scores and defined as Grade 0 of ≤ 0.3, Grade 1 of ≤ 1.1, Grade 2a of ≤ 2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0.

The proportion of patients in UC-1 and UC-2 achieving a clinical response was 66.5% and 53.1%, respectively, for patients receiving filgotinib 200 mg compared with 46.7% and 17.6%, respectively, for patients receiving placebo at week 10.

In the maintenance study (UC-3), a significantly greater proportion of patients receiving filgotinib 200 mg or filgotinib 100 mg achieved clinical remission at week 58 as compared to placebo. The proportion of patients achieving clinical remission is shown in Table 7. A significantly greater proportion of patients receiving filgotinib 200 mg achieved MCS remission, sustained clinical remission, 6-month corticosteroid-free clinical remission, endoscopic remission, and histologic remission at week 58 as compared to placebo.

Key secondary efficacy outcomes for treatment with filgotinib 100 mg as compared to placebo were not statistically significant at week 58.

Table 7: Proportion of patients meeting efficacy endpoints at week 58 in maintenance study UC-3

Endpoint n (%)	Induction FIL 200 mg		
	FIL 200 mg N = 199	Placebo N = 98	Treatment difference and 95% CI
Clinical remission [a b]	74 (37.2%)	11 (11.2%)	26.0% (16.0%, 35.9%) p < 0.0001
Biologic naïve	52/107 (48.6%)	9/54 (16.7%)	-
Biologic experienced	22/92 (23.9%)	2/44 (4.5%)	-
MCS remission [c]	69 (34.7%)	9 (9.2%)	25.5% (16.0%, 35.0%) p < 0.0001
Sustained clinical remission [d b]	36 (18.1%)	5 (5.1%)	13.0% (5.3%, 20.6%) p = 0.0024
Biologic naïve	25/107 (23.4%)	4/54 (7.4%)	-
Biologic experienced	11/92 (12.0%)	1/44 (2.3%)	-
6-month corticosteroid-free clinical remission [e b]	25/92 (27.2%)	3/47 (6.4%)	20.8% (7.7%, 33.9%) p = 0.0055
Biologic naïve	18/43 (41.9%)	2/22 (9.1%)	-
Biologic experienced	7/49 (14.3%)	1/25 (4.0%)	-
Endoscopic remission [f]	31 (15.6%)	6 (6.1%)	9.5% (1.8%, 17.1%) p = 0.0157
Histologic remission [g]	76 (38.2%)	13 (13.3%)	24.9% (14.6%, 35.2%) p < 0.0001

CI: Confidence interval; FIL: filgotinib; MCS: Mayo Clinic Score.

a Primary endpoint. Clinical remission was defined as MCS endoscopy subscore of 0 or 1 (endoscopy subscore of 0 defined as normal or inactive disease and subscore of 1 defined as presence of erythema, decreased vascular pattern, and no friability), rectal bleeding subscore of 0 (no rectal bleeding), and at least a one point decrease in stool frequency subscore from induction baseline to achieve 0 or 1.

b Subgroup analysis based on patient participation in UC-1 (biologic naïve) or UC-2 (biologic experienced; TNF blocker and/or vedolizumab).

c MCS remission was defined as MCS ≤ 2 with no individual subscore of > 1.

d Sustained clinical remission was defined as clinical remission at both week 10 and week 58.

e 6-month corticosteroid-free clinical remission was defined as clinical remission at week 58 in patients who were on corticosteroid at UC-3 baseline and who were not receiving corticosteroids for at least 6 months prior to week 58.

f Endoscopic remission was defined as MCS endoscopic subscore of 0.

g Histologic remission was assessed using Geboes histologic scores and defined as Grade 0 of ≤ 0.3, Grade 1 of ≤ 1.1, Grade 2a of ≤ 2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0.

Endoscopic response

Endoscopic response was defined as an endoscopic subscore of 0 or 1. The proportion of patients in UC-1 and UC-2 achieving an endoscopic response was 33.9% and 17.2%, respectively, for patients receiving filgotinib 200 mg compared with 20.4% and 7.7%, respectively, for patients receiving placebo, at week 10. In UC-3, 40.7% of patients receiving filgotinib 200 mg *versus* 15.3% of patients receiving placebo achieved endoscopic response at week 58.

Health-related quality of life (HRQoL) outcomes

Patients receiving filgotinib 200 mg reported increases (improvements) in the total and all four domain scores of the Inflammatory Bowel Disease Questionnaire ([IBDQ] bowel symptoms, systemic

function, emotional function, and social function) at week 10 in UC-1 and UC-2, and at week 58 in UC-3.

Long-term extension study
Patients who did not achieve clinical response or remission at week 10 in UC-1 or UC-2 had the option to receive open-label filgotinib 200 mg in the SELECTION LTE study. After 12 weeks of additional treatment with filgotinib 200 mg in the SELECTION LTE study, the proportion of patients from UC-1 and UC-2 achieving partial MCS remission was 17.1% (12/70) and 16.7% (15/90), respectively and partial MCS response was achieved by 65.7% (46/70) and 62.2% (56/90), respectively. Partial MCS remission was defined as partial MCS ≤ 1 and partial MCS response was defined as a reduction of ≥ 2 in partial MCS and at least 30% reduction from the induction baseline score, with an accompanying decrease of ≥ 1 in the rectal bleeding subscore or an absolute rectal bleeding subscore of 0 or 1.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with filgotinib in one or more subsets of the paediatric population in the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, ankylosing spondylarthritis, psoriatic arthritis, and juvenile idiopathic arthritis) and in ulcerative colitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral administration, filgotinib was absorbed quickly and its median peak plasma concentration was observed 2 to 3 hours postdose after multiple dosing; the median peak plasma concentrations of its primary metabolite GS-829845 were observed 5 hours postdose after multiple dosing. Filgotinib and GS-829845 exposures (AUC) and C_{max} were similar in healthy adult subjects and patients with rheumatoid arthritis and ulcerative colitis. Filgotinib and GS-829845 exposures (AUC) and C_{max} are dose-proportional over the therapeutic dose range. Steady-state concentrations of filgotinib are achieved in 2 - 3 days with negligible accumulation after once daily administration. Steady-state concentrations of GS-829845 are achieved in 4 days with approximately 2-fold accumulation after once daily dosing of filgotinib.

There were no clinically relevant differences in exposures when filgotinib was administered with a high-fat or low-fat meal as compared to a fasted state. Filgotinib can be administered with or without food.

Steady-state exposures of filgotinib and GS-829845 are provided in Table 8.

Table 8: Multiple dose pharmacokinetic parameters of filgotinib and GS-829845 following oral administration of filgotinib 200 mg with or without food in patient populations

	Rheumatoid arthritis [a]		Ulcerative colitis [b]	
Parameter Mean (%CV)	**Filgotinib [c]**	**GS-829845 [d]**	**Filgotinib**	**GS-829845**
C_{max} (µg/mL)	2.15 (48.1)	4.43 (29.3)	2.12 (50.3) [e]	4.02 (30.5) [e]
AUC_{tau} (µg•h/mL)	6.77 (43.7)	83.2 (27.3)	6.15 (28.1) [f]	72.1 (33.9) [g]

CV: coefficient of variation.
a From intensive PK analyses of studies FINCH 1, FINCH 2, and FINCH 3 in rheumatoid arthritis patients receiving 200 mg filgotinib once daily.
b From intensive PK analysis of SELECTION study in ulcerative colitis patients receiving 200 mg filgotinib once daily.
c N = 37
d N = 33
e N = 13
f N = 12
g N = 11

Distribution

Filgotinib and GS-829845 binding to human plasma proteins is low (55 - 59% and 39 - 44% bound, respectively). The blood-to-plasma ratio of filgotinib ranged from 0.85 to 1.1 indicating no preferential distribution of filgotinib and GS-829845 into blood cells. Filgotinib and GS-829845 are substrates of the P-gp transporter.

Biotransformation

Filgotinib is extensively metabolised with approximately 9.4% and 4.5% of an orally administered dose recovered as unchanged filgotinib in urine and faeces, respectively. Filgotinib is primarily metabolised by CES2, and to a lesser extent by CES1. Both CES2 and CES1 form GS-829845, an active circulating metabolite that is approximately 10-fold less potent than the parent compound. In a clinical pharmacology study, filgotinib and GS-829845 accounted for the majority of radioactivity circulating in plasma (2.9% and 92%, respectively). No other major metabolites were identified.

As both filgotinib and GS-829845 contribute to efficacy, their exposures were combined into a single parameter, AUC_{eff}. AUC_{eff} is the sum of the AUC of filgotinib and GS-829845, corrected for their respective molecular weights and potencies.

Elimination

Approximately 87% of the administered dose was eliminated in the urine as filgotinib and its metabolites, while about 15% of the dose was eliminated in the faeces. GS-829845 accounted for approximately 54% and 8.9% of dose recovered in urine and faeces, respectively. The mean terminal half-lives of filgotinib and GS-829845 were approximately 7 and 19 hours, respectively.

Other special populations

Weight, gender, race, and age
Bodyweight, gender, race, and age did not have a clinically relevant effect on the pharmacokinetics (AUC) of filgotinib or GS-829845.

Elderly
There were no clinically relevant differences in mean filgotinib and GS-829845 exposures (AUC and C_{max}) between older patients aged ≥ 65 years relative to adult patients aged < 65 years.

Renal impairment
The pharmacokinetics of filgotinib and GS-829845 were unaffected in subjects with mild renal impairment (CrCl 60 to < 90 mL/min). Increases in exposures (AUC) of filgotinib, GS-829845, and combined AUC_{eff} (≤ 2-fold), were observed in subjects with moderate renal impairment (CrCl 30 to < 60 mL/min). In subjects with severe renal impairment (CrCl 15 to < 30 mL/min), filgotinib exposure (AUC) increased by 2.2-fold and GS-829845 exposure significantly increased by 3.5-fold leading to a 3-fold increase in AUC_{eff}. The pharmacokinetics of filgotinib has not been studied in subjects with end stage renal disease (CrCl < 15 mL/min).

Hepatic impairment
No clinically relevant changes in the exposures (AUC) of filgotinib and GS-829845 individually, or their combined exposure (AUC_{eff}), were observed in subjects with moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of filgotinib has not been studied in subjects with severe hepatic impairment (Child-Pugh C).

Effect of filgotinib on other medicinal products

Potential interactions between filgotinib and co-administered medicinal products are listed in Table 9 below (increase is indicated as "↑", decrease as "↓", and no change as "↔"; no effect boundaries are 70 - 143% unless otherwise indicated).

Table 9: Interaction studies with filgotinib [1]

Medicinal product by therapeutic areas/Possible mechanism of interaction	Effects on medicinal product levels. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with filgotinib
ANTI-INFECTIVES		
Antimycobacterials		
Rifampicin (600 mg once daily) [2] (P-gp induction)	Filgotinib: AUC: ↓ 27% C_{max}: ↓ 26% GS-829845: AUC: ↓ 38% C_{max}: ↓ 19% AUC_{eff} [6]: ↓ 33%	No dose adjustment is required upon co-administration.
Antifungals		
Itraconazole (200 mg single dose) [3] (P-gp inhibition)	Filgotinib: AUC: ↑ 45% C_{max}: ↑ 64% GS-829845: AUC: ↔ C_{max}: ↔ AUC_{eff}: ↑ 21%	No dose adjustment is required upon co-administration.
GASTRIC ACID REDUCING AGENTS		
Famotidine (40 mg twice daily) [2] (Increases gastric pH)	Filgotinib: AUC: ↔ C_{max}: ↔ GS-829845: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.
Omeprazole (40 mg once daily) [2] (Increases gastric pH)	Filgotinib: AUC: ↔ C_{max}: ↓ 27% GS-829845: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.
HMG-CoA REDUCTASE INHIBITORS		
Atorvastatin (40 mg single dose) [4] (Inhibition of CYP3A4/ OATP/BCRP)	Atorvastatin: AUC: ↔ C_{max}: ↓ 18% 2-hydroxy-atorvastatin: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.
Pravastatin (40 mg single dose) [4] (Inhibition of OATP)	Pravastatin: AUC: ↔ C_{max}: ↑ 25%	No dose adjustment is required upon co-administration.

Medicinal product by therapeutic areas/Possible mechanism of interaction	Effects on medicinal product levels. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with filgotinib
Rosuvastatin (10 mg single dose) [4] (Inhibition of OATP and BCRP)	Rosuvastatin: AUC: ↑ 42% C_{max}: ↑ 68%	No dose adjustment is required upon co-administration.
ORAL ANTI-DIABETICS		
Metformin (850 mg single dose) [4] (Inhibition of OCT2, MATE1, and MATE-2K)	Metformin: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.
ORAL CONTRACEPTIVES		
Ethinyl estradiol (0.03 mg single dose)/Levonorgestrel (0.15 mg single dose) [4]	Ethinyl estradiol: AUC: ↔ C_{max}: ↔ Levonorgestrel: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.
SEDATIVES/HYPNOTICS		
Midazolam (2 mg single dose) [4,5] (Inhibition of CYP3A4)	Midazolam: AUC: ↔ C_{max}: ↔ 1'OH-midazolam: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.

GS-829845: primary metabolite of filgotinib.
1 All interaction studies conducted in healthy volunteers.
2 Study conducted with filgotinib 200 mg single dose.
3 Study conducted with filgotinib 100 mg single dose.
4 Study conducted with filgotinib 200 mg once daily.
5 Bioequivalence boundaries are 80 - 125% for midazolam and 1'OH-midazolam.
6 As both filgotinib and GS-829845 contribute to efficacy, their exposures were combined into a single parameter, AUC_{eff}. AUC_{eff} is the combined AUC of filgotinib and GS-829845, adjusted for their respective molecular weights and potencies.

Potential for filgotinib to affect other medicinal products
In vitro data indicate that filgotinib and GS-829845 do not inhibit the activity of the following: CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 at clinically relevant concentrations. The potential for filgotinib to induce CYP2B6 constitutive androstane receptor (CAR) mediated metabolism *in vivo* is unknown. No conclusion can be drawn from the *in vitro* data regarding the potential of filgotinib to inhibit or induce CYP1A2.
In vivo data demonstrated no inhibition or induction of CYP3A4 mediated metabolism.

In vitro studies indicate that filgotinib and GS-829845 are not inhibitors of P-gp, BCRP, OCT1, BSEP, OAT1, OAT3 or OAT4 at clinically relevant concentrations.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology.

The carcinogenic potential of filgotinib was evaluated in a 6-month rasH2 transgenic mouse study and a 2-year rat study. Filgotinib was not carcinogenic in mice at up to 150 mg/kg/day, which resulted in exposures of approximately 25 and 12 times the exposures in humans at the 100 mg and 200 mg once daily doses, respectively. In the 2-year rat study, filgotinib treatment resulted in an increase in incidence and decrease in latency of benign Leydig cell tumours at the highest dose of 45 mg/kg/day (exposures of approximately 4.2 times exposures in humans at the 200 mg once daily dose); the clinical relevance of this finding is low.

Filgotinib was not mutagenic or clastogenic in the *in vitro* bacterial reverse mutation assay, *in vitro* chromosome aberration assay, and *in vivo* rat micronucleus assay.

Adverse findings of degeneration/necrosis of incisor ameloblasts were observed in rats at exposures 21- to 28-fold greater than clinical exposures at the 200 mg filgotinib dose, with exposure margins at the no-observed-adverse-effect-level (NOAEL) ranging from 3.5- to 8-fold. The human relevance of these dental findings is considered low since in contrast to adult patients, ameloblasts in rats persist into adulthood to support lifelong continuous incisor growth.

Impaired spermatogenesis and histopathological effects on male reproductive organs (testes and epididymis) were observed with filgotinib in rats and dogs. At the NOAELs in dogs (the most sensitive species), the exposure margin is 2.7-fold at the 200 mg once daily dose in humans. The severity of the histological effects was dose-dependent. Spermatogenic and histopathological effects were not fully reversible at exposure margins of approximately 7- to 9-fold the exposure at the 200 mg once daily dose in humans.

Embryo-foetal development studies in rats and rabbits demonstrated embryolethality and teratogenicity at exposures comparable to 200 mg filgotinib once daily dosing in humans. Visceral and skeletal malformations and/or variations were observed at all dose levels of filgotinib.

Filgotinib was administered to pregnant rats at doses of 25, 50, and 100 mg/kg/day. Dose-related increases in the incidence of internal hydrocephaly, dilated ureters, and multiple vertebral anomalies were seen at all dose levels. At 100 mg/kg/day, an increased number of early and late resorptions were noted together with a decreased number of viable foetuses. In addition, foetal body weights were decreased.

In rabbits, filgotinib caused visceral malformations mainly in the lungs and cardiovascular system, at a dose level of 60 mg/kg/day. Filgotinib caused skeletal malformations affecting the vertebral column region at dose levels of 25 and 60 mg/kg/day, mainly in vertebra, ribs and sternebrae. Fused sternebrae also occurred at 10 mg/kg/day filgotinib. Retarded skeletal ossification was evidenced at 60 mg/kg/day.

No adverse effects on pre-/postnatal development were observed in rats in a pre- and postnatal development study of filgotinib and GS-829845. Filgotinib and GS-829845 were detected in nursing rat pups after administration of filgotinib to lactating female rats from gestation day 6 through 10 days post-partum at dose levels of 2, 5, and 15 mg/kg/day, likely due to the presence of filgotinib in milk. At the highest tested dose, maternal systemic exposure (AUC) to filgotinib in rats was approximately 2 times the exposure in humans at the 200 mg once daily dose; exposures in nursing pups were less than 6% that of maternal exposure on day 10 post-partum. Due to the low exposure of the animals, the pre-/postnatal development study was considered inconclusive.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Lactose monohydrate
Pregelatinised starch
Colloidal silicon dioxide
Fumaric acid
Magnesium stearate

Film-coating

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

White, high-density polyethylene (HDPE) bottles, enclosed with a child-resistant polypropylene (PP) screw cap lined with an induction-sealed aluminium foil liner. Each bottle contains either a canister or sachet containing silica gel desiccant and polyester coil.

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets and outer cartons containing 90 (3 bottles of 30) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Galapagos NV
Generaal De Wittelaan L11 A3
2800 Mechelen
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Jyseleca 100 mg film-coated tablets

EU/1/20/1480/001
EU/1/20/1480/002

Jyseleca 200 mg film-coated tablets

EU/1/20/1480/003
EU/1/20/1480/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 September 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Galapagos NV
Generaal De Wittelaan L11 A3
2800 Mechelen
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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), 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:

- Summary of Product Characteristics
- 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 patient alert card 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 deep venous thrombosis or pulmonary embolism 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON LABELLING FOR 100 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jyseleca 100 mg film-coated tablets
filgotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg filgotinib (as maleate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

90 (3 bottles of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

QR code to be included
www.jyseleca.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. **Keep the bottle tightly closed.**

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Galapagos NV
Gen. De Wittelaan L11 A3
2800 Mechelen
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1480/001 30 film-coated tablets
EU/1/20/1480/002 90 (3 bottles of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jyseleca 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABELLING FOR 100 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jyseleca 100 mg film-coated tablets
filgotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg filgotinib (as maleate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. **Keep the bottle tightly closed.**

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Galapagos NV
Gen. De Wittelaan L11 A3
2800 Mechelen
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1480/001 30 film-coated tablets
EU/1/20/1480/002 90 (3 bottles of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON LABELLING FOR 200 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jyseleca 200 mg film-coated tablets
filgotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg filgotinib (as maleate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

90 (3 bottles of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

QR code to be included
www.jyseleca.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. **Keep the bottle tightly closed.**

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Galapagos NV
Gen. De Wittelaan L11 A3
2800 Mechelen
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1480/003 30 film-coated tablets
EU/1/20/1480/004 90 (3 bottles of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jyseleca 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABELLING FOR 200 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jyseleca 200 mg film-coated tablets
filgotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg filgotinib (as maleate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. **Keep the bottle tightly closed.**

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Galapagos NV
Gen. De Wittelaan L11 A3
2800 Mechelen
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1480/003 30 film-coated tablets
EU/1/20/1480/004 90 (3 bottles of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Jyseleca 100 mg film-coated tablets
Jyseleca 200 mg film-coated tablets
filgotinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Jyseleca is and what it is used for

Jyseleca contains the active substance filgotinib. It belongs to a group of medicines called Janus kinase inhibitors, which help reduce inflammation.

Rheumatoid arthritis
Jyseleca is used to treat adults with rheumatoid arthritis, an inflammatory disease of the joints. It can be used if previous therapy did not work well enough, or was not tolerated. Jyseleca can be used on its own, or together with another arthritis medicine, methotrexate.

Jyseleca reduces inflammation in your body. It helps to reduce pain, tiredness, stiffness and swelling in your joints, and it slows down damage to the bone and cartilage in the joints. These effects can help you to perform your normal daily activities, and improve your quality of life.

Ulcerative colitis
Jyseleca is used to treat adults with ulcerative colitis, an inflammatory disease of the bowel. It can be used if you did not respond well enough or did not tolerate previous therapy. It helps to reduce the signs and symptoms of ulcerative colitis and to reduce your need for steroids.

2. What you need to know before you take Jyseleca

Do not take Jyseleca
- **if you are allergic** to filgotinib or any of the other ingredients of this medicine (listed in section 6).
- **if you have active tuberculosis (TB).**

- **if you have an active serious infection** (see section "Warnings and precautions").
- **if you are pregnant** or think you may be pregnant.

➔ If any of these apply to you, **do not take Jyseleca and tell your doctor immediately.**

Warnings and precautions
Talk to your doctor or pharmacist before taking Jyseleca:
- **if you have an infection,** or if you often get infections. Tell your doctor if you get symptoms such as fever, wounds, feeling more tired than usual or dental problems as these can be signs of infection. Jyseleca can reduce your body's ability to fight infections and may make an existing infection worse or increase the chance of you getting a new infection. If you have diabetes or are aged 65 years or older you may have an increased chance of getting infections.
- **if you have ever had tuberculosis (TB),** or have come into contact with somebody with TB. You may need tests to check for tuberculosis before and during treatment with Jyseleca.
- **if you have had a herpes zoster infection (shingles)** in the past, Jyseleca can allow it to come back. Tell your doctor if you get a painful skin rash with blisters during Jyseleca treatment as these can be signs of shingles.
- **if you have ever had hepatitis B or C.**
- **if you have or have had cancer, smoke or have smoked in the past**, because your doctor will discuss with you if Jyseleca is appropriate for you.
- **Non-melanoma skin cancer has been observed in patients taking Jyseleca.** Your doctor may recommend that you have regular skin examinations while taking Jyseleca. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.
- **if you recently had a vaccine,** or are due to have one. Certain types of vaccines (live vaccines) are not recommended while using Jyseleca. Talk to your doctor or pharmacist before you start Jyseleca. They may want to make sure that you are up to date with your vaccinations.
- **if you have, or have had, heart problems**, because your doctor will discuss with you if Jyseleca is appropriate for you.
- **if you have previously had blood clots** in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism) or have an increased risk for developing this (for example: if you had a recent major surgery, if you use hormonal contraceptives\hormonal replacement therapy, if a coagulation defect is identified in you or your close relatives). Your doctor will discuss with you if Jyseleca is appropriate for you. Tell your doctor if you get sudden shortness of breath or difficulty breathing, chest pain or pain in upper back, swelling of the leg or arm, leg pain or tenderness, or redness or discoloration in the leg or arm as these can be signs of blood clots in the veins.

Elderly

Patients aged 65 years and older may be at increased risk of infections, heart attack and some types of cancer. Your doctor may decide that Jyseleca is not suitable for you.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years of age because it has not been studied in this age group.

Other medicines and Jyseleca
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, especially if you use medicines that affect your immune system (such as ciclosporin or tacrolimus).
It is also very important to talk to your doctor or pharmacist if you are taking any of the following:
- medicines to treat heart failure, coronary disease or high blood pressure (such as diltiazem or carvedilol)
- the medicine fenofibrate (used to treat high cholesterol)

Pregnancy, contraception and breast-feeding
Pregnancy
Jyseleca must not be used in pregnancy. If you are pregnant, think you may be pregnant or if you are planning to have a baby, do not take this medicine. Talk to your doctor for advice.

Contraception
Be careful not to get pregnant while you are taking Jyseleca. You must use reliable contraception while you are taking Jyseleca, and for at least 1 week after you take your last dose of Jyseleca. If you do become pregnant while you are taking Jyseleca, stop taking the tablets and tell your doctor immediately.

Breast-feeding
Do not breast-feed while you are taking Jyseleca. It is not known whether the active substance passes into human breast milk.

Driving and using machines
Jyseleca can cause dizziness. If you feel dizzy when taking Jyseleca, do not drive and do not use any tools or machines.

Jyseleca contains lactose
Each Jyseleca 100 mg film-coated tablet contains 76 mg of lactose, and each Jyseleca 200 mg film-coated tablet contains 152 mg of lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Jyseleca

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 200 mg or 100 mg tablet once a day.

If you are aged 65 years of age or older with rheumatoid arthritis or if you have kidney problems, your doctor may recommend a dose of one 100 mg tablet once a day. Jyseleca is not recommended for you if you are over 75 years old with ulcerative colitis. Talk to your doctor if you have severe liver problems, as Jyseleca is not recommended for you.

Swallow your tablet with a glass of water. Do not split, crush, or chew the tablet before swallowing as it may change how much medicine gets into your body. You can take Jyseleca with food or between meals. Do not swallow the desiccant.

Take Jyseleca at the same time every day. This will help you to remember to take the tablets.

Your doctor may stop treatment temporarily or permanently if blood tests show a low white or red blood cell count.

If you take more Jyseleca than you should
If you take more tablets than you should, tell your doctor straight away.

If you forget to take Jyseleca
- If you miss a dose, take it as soon as you remember.
- If you have gone a whole day (24 hours) without taking a dose, just skip the missed dose and take a single dose at your usual time.
- Do not take a double dose to make up for a forgotten tablet.

If you stop taking Jyseleca
If you stop taking Jyseleca, tell your doctor straight away.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Talk to your doctor or get medical help straight away if you get any signs of serious infection such as:
- fever and symptoms of urinary tract infection (urinating more frequently than usual, pain or discomfort when urinating or back pain). Urinary tract infections are common (may affect up to 1 in 10 people), and some of these may be serious.
- lung infection (pneumonia): symptoms can include persistent cough, fever, shortness of breath, and tiredness. This is uncommon (may affect up to 1 in 100 people).
- shingles (herpes zoster): symptoms can include a painful skin rash with blisters. This is uncommon (may affect up to 1 in 100 people).
- Blood infection (sepsis): uncommon (may affect up to 1 in 100 people)

Other side effects
Talk to your doctor if you notice any of the following side effects:

Common
(may affect up to 1 in 10 people)
- throat and nose infections
- dizziness
- feeling sick (nausea)

Blood tests may show:
- a low number of white blood cells (lymphocytes).

Uncommon
(may affect up to 1 in 100 people)

Blood tests may show:
- a low number of white blood cells (neutrophils)
- an increase in a muscle enzyme called creatine phosphokinase
- an increased level of blood fat (cholesterol).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Jyseleca

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not use this medicine if you notice that the seal over the bottle opening is broken or missing.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Jyseleca contains

- The active substance is filgotinib. Each film-coated tablet contains 100 or 200 mg of filgotinib (as filgotinib maleate).

- The other ingredients are:
  Tablet core: microcrystalline cellulose, lactose monohydrate, pregelatinised starch, colloidal silicon dioxide, fumaric acid, magnesium stearate
  Film-coating: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide yellow (E172), iron oxide red (E172)

What Jyseleca looks like and contents of the pack
Jyseleca 100 mg film-coated tablets are beige, 12 mm × 7 mm in size, capsule-shaped with “G” on one side and “100” on the other.

Jyseleca 200 mg film-coated tablets are beige, 17 mm × 8 mm in size, capsule-shaped with “G” on one side and “200” on the other.

Jyseleca 100 mg and 200 mg are available in bottles of 30 tablets and in packs made up of 3 bottles, each containing 30 tablets. Each bottle contains a silica gel desiccant that must be kept in the bottle to help protect your tablets. The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

QR code to be included