EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/424374/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jyseleca

International non-proprietary name: filgotinib

Procedure No. EMEA/H/C/005113/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACR20	American College of Rheumatology 20% improvement
AE	adverse event
AEI	adverse event of interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under curve
BCS	Biopharmaceutics classification system
bDMARD	biologic disease-modifying antirheumatic drug
BID	twice daily
BP	blood pressure
CIA	collagen induced arthritis
CHMP	Committee for Medicinal Products for Human use
CPP	Critical process parameter
CQA	Critical quality attribute
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVD	cardiovascular disease
CVEAC	cardiovascular safety endpoint adjudication committee
CYP	cytochrome P450 enzyme
DoE	Design of experiments
DSC	Differential scanning calorimetry
DVS	Dynamic vapour sorption
DVT	deep vein thrombosis
EC	European Commission
ECG	electrocardiogram
ELISA	Enzyme linked immunosorbent assay
EPO	erythropoietin
FAS	Full Analysis Set

FMEA	Failure mode effects analysis
FSH	follicle-stimulating hormone
GC	Gas chromatography
GGT	gamma-glutamyltransferase
GI	gastrointestinal
HAQ-DI	Health Assessment Questionnaire-Disability Index
HDL	high-density lipoprotein
HDPE	High density polyethylene
HI	Hepatic impairment
HPLC	High performance liquid chromatography
HR	heart rate
IC50	half max inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
Ig	Immunoglobulin
IL-6	interleukin 6
IPC	In-process control
IR	inadequate responder
IR	Infrared
ITT	intent-to-treat
JAK	Janus kinase
LDL	low-density lipoprotein
LH	luteinizing hormone
LOCF	last observation carried forward
LTE	long-term extension
MAA	marketing authorization application
MACE	major adverse cardiac event
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NF	National formulary
NK	natural killer
NMR	Nuclear magnetic resonance
NMSC	nonmelanoma skin cancer(s)

NOAEL	No Observed Adverse Effect Level
NOEC	no observed effect concentration
NRI	nonresponder imputation
NSAID	nonsteroidal anti-inflammatory drug
OC	observed case
PAR	Proven acceptable range
PD	pharmacodynamic(s)
PDE	Permitted daily exposure
PE	pulmonary embolism
Ph. Eur.	European Pharmacopoeia
PJP	Pneumocystis jirovecii pneumonia
PK	pharmacokinetic(s)
PP	per protocol
PP	Polypropylene
PT	preferred term
PY	person-year
PYE	patient-years of exposure
Q1	first quartile
Q3	third quartile
QbD	Quality by design
QC	Quality control
QD	once daily
QSAR	Quantitative structure-activity relationship
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QW	once weekly
RA	Rheumatoid arthritis
RH	Relative humidity
RI	Renal impairment
RMSE	Root mean square error
SAE	serious adverse event
SAP	statistical analysis plan

SC	subcutaneous
SD	standard deviation
SmPC	Summary of product characteristics
SOC	system organ class
SP	safety pharmacology
STAT	signal transducer and activator of transcription
TB	tuberculosis
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TTC	Threshold of toxicological concern
TYK	tyrosine kinase
ULN	upper limit of normal
USP	United States Pharmacopoeia
UTI	urinary tract infection
UV	Ultraviolet
VTE	venous thromboembolism
WBC	white blood cell
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences Ireland UC submitted on 24 July 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Jyseleca, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 June 2018.

The applicant applied for the following indication: *"Jyseleca is indicated as monotherapy or in combination with methotrexate (MTX) or other conventional synthetic disease modifying antirheumatic drugs (csDMARDs) for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant to, one or more DMARDs.*

Jyseleca is indicated as monotherapy for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have highly active and early progressive (erosive) disease, were not previously treated with MTX, and for whom treatment with MTX is inappropriate."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0371/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance filgotinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
20 September 2012	EMEA/H/SA/2380/1/2012/III	*Dr C. Auriche, Prof. B. Bloechl-Daum, Dr K. Gudmundsson*
23 July 2015	EMEA/H/SA/2380/1/FU/1/2015/III	*Prof. D. Deforce, Dr K. Gudmundsson*
1 April 2016	EMEA/H/SA/2380/1/FU/2/2016/III	*Dr F. Torres, Dr P. Kiely*

The Scientific Advice pertained to the following quality, pre-clinical and clinical aspects:

- Acceptability of the proposed dissolution method for the finished product tablet and the proposed dissolution specifications
- Acceptability of the proposed regulatory starting materials for the commercial synthesis of the drug substance
- Adequacy of the control strategy for potential genotoxic impurities proposed for the drug substance manufacturing process.
- Appropriateness of the proposed drug substance and finished product specification parameters
- Acceptability of the proposed bracketing approach for the investigation of drug product stability
- Acceptability of the overall toxicology plan and the timing of the planned toxicology studies
- Appropriateness of the planned non-clinical safety programme and in particular of the planned 13-week toxicity studies in rats and dogs to characterise the safety profile of the drug substance and its main metabolite
- Appropriateness of the proposed juvenile toxicity study in rats to support paediatric development
- Appropriateness of the planned drug-drug-interaction studies
- Acceptability of the proposed safety monitoring in early clinical studies in healthy volunteers and patients with rheumatoid arthritis regarding the risk of immunosuppression and potential effects on the male reproductive system
- Need for a relative bioavailability study comparing phase 2 formulations and the phase 3 tablet formulation
- Acceptability of the proposed dose regimen for testing in phase 3 clinical studies
- Appropriateness of the plans for a global phase 3 development programme to demonstrate efficacy and safety: one study in MTX inadequately responsive patients and one study in biological DMARD inadequately responsive patients
- Appropriateness of a proposed phase 3 placebo- and active-controlled study in moderate to severe RA patients as add-on to MTX: overall study design, study population, primary and secondary efficacy endpoints, selection of active comparator, choice of non-inferiority margin vs. active comparator and sample size

- Appropriateness of a proposed phase 3 placebo-controlled study in moderate to severe RA patients with inadequate response to biological DMARD treatment: overall study design, study population, primary and secondary efficacy endpoints and sample size
- Appropriateness of the planned safety monitoring in phase 3 clinical studies
- Adequacy of the envisaged size of the overall safety database
- Appropriateness of a proposed phase 1 study to investigate testicular safety
- Need to characterise pharmacokinetics (PK) in patients with hepatic impairment

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Jean-Michel Race

The application was received by the EMA on	24 July 2019
The procedure started on	15 August 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	4 November 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	5 November 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 November 2019
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	28 November 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 December 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	11 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 May 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	28 May 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 June 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	08 July 2020
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 July 2020

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Jyseleca on	23 July 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication initially proposed by the applicant was as follows:

"Jyseleca is indicated as monotherapy or in combination with methotrexate (MTX) or other conventional synthetic disease modifying antirheumatic drugs (csDMARDs) for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant to, one or more DMARDs.

Jyseleca is indicated as monotherapy for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have highly active and early progressive (erosive) disease, were not previously treated with MTX, and for whom treatment with MTX is inappropriate."

2.1.2. Epidemiology

Rheumatoid arthritis (RA) is a chronic, incurable, systemic autoimmune inflammatory disease that affects about 1% of the adult population worldwide, with onset typically between the ages of 30 and 50 years, and a 2- to 3-fold higher prevalence in women. The disease is characterized by chronic inflammation of the joints, occurring in the synovial tissue and manifesting in swelling, pain, stiffness, and restricted mobility. This inflammation may be associated with the destruction of articular cartilage and juxta-articular bone, causing irreversible joint damage (Firestein 2003, Smolen 2007, Smolen 2016a). Rheumatoid arthritis is also associated with extra-articular manifestations that may involve the skin, eyes, salivary glands, and lungs. Lung involvement may include interstitial lung disease, which is responsible for significant morbidity and mortality (Olson 2011, Raimundo 2019). Cardiovascular disease (CVD) is markedly increased in patients with RA, in part due to accelerated atherosclerosis from chronic inflammation. Traditional cardiovascular risk factors such as hypertension, hyperlipidaemia, smoking, diabetes mellitus, and physical inactivity are also highly prevalent among patients with RA and contribute to the increased CVD risk (Crowson 2018, Gonzalez 2008, Solomon 2010).

2.1.3. Biologic features, Aetiology and pathogenesis

The aetiology of RA is unknown, although genetic, environmental, and lifestyle factors (such as smoking) have been identified as contributors, and the development of inflammation is associated with loss of tolerance to self-antigens (Aletaha 2018, Smolen 2016b). The disease pathophysiology is heterogeneous, with joint inflammation and destruction driven by interactions between multiple resident cells and infiltrating immune cells, leading to propagation and maintenance of a pro-inflammatory cytokine response, a key driver of the disease.

2.1.4. Clinical presentation, diagnosis

The disease is characterized by chronic inflammation of the joints manifesting in swelling, pain, stiffness, and restricted mobility. This inflammation may be associated with irreversible joint damage and there are also extra-articular manifestations (see further above).

The RA diagnosis is based on careful history and clinical examination, guided by additional procedures such as laboratory testing. Erosions detected by X-ray and positivity for antibodies against cyclic citrullinated peptide (anti-CCP) or Rheumatoid Factor (RF) are factors associated with poor prognosis.

2.1.5. Management

According to EULAR (European League Against Rheumatism) recommendations (EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update), treatment should be initiated as soon as the RA diagnosis is made. Treatment should be aimed at reaching a target of sustained low disease activity. Methotrexate (MTX) should be the first treatment strategy. In patients with contraindications to MTX (or early intolerance), leflunomide or sulfalazine should be considered as the (first) line treatment strategy. If there is no improvement by at most 3 months after start of treatment or the target has not been reached by 6 months, therapy should be adjusted. Depending on whether poor prognostic factors are present or not, other csDMARD or addition of a bDMARD (biologic DMARD) or tsDMARD (targeted synthetic DMARD) could then be considered. JAK-inhibitors are tsDMARD.

Despite the recent advances in this therapeutic field, there all still patients who either cannot tolerate or do not respond to the available treatment options i.e. there is still an unmet need.

About the product

Filgotinib is a new JAK-inhibitor initially intended for 1st, 2nd and 3rd line treatment of RA either as monotherapy or as combination therapy (see above for claimed indication). The proposed posology was 200 mg once daily (100 mg once daily for patients with severe renal impairment).

Type of Application and aspects on development

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing filgotinib maleate as active substance, equivalent to 100 mg or 200 mg of filgotinib free base.

Other ingredients are:

Tablet core: microcrystalline cellulose, lactose monohydrate, pregelatinized starch, colloidal silicon dioxide, fumaric acid and magnesium stearate;

Film-coating: polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide yellow and iron oxide red.

The product is available in white, high-density polyethylene (HDPE) bottles, closed with a child-resistant polypropylene (PP) screw cap lined with an induction-sealed aluminium foil liner and containing either a canister or sachet of desiccant as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of filgotinib maleate is *N*-(5-{4-[(1,1-Dioxidothiomorpholin-4-yl) methyl]phenyl}[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide (2*Z*)-but-2-enedioate corresponding to the molecular formula $C_{21}H_{23}N_5O_3S.C_4H_4O_4$. It has a relative molecular mass of 541.6 g/mol and the following structure:

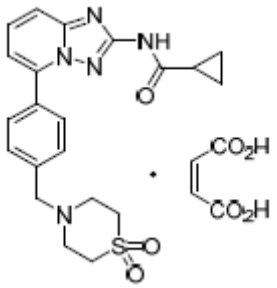


Figure 1: active substance structure

The chemical structure of filgotinib maleate was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, elemental analysis, infrared spectroscopy and single crystal x-ray crystallography. The solid-state properties of the active substance were measured by differential scanning calorimetry (DSC), dynamic vapour sorption (DVS) and x-ray powder diffraction (XRPD).

Filgotinib maleate is a white to off-white achiral, slightly hygroscopic crystalline salt with three ionizable nitrogens exhibiting pH-dependent solubility in aqueous media. It is slightly soluble at pH 2 but practically insoluble at pH 5-7. A single polymorphic form was identified during development although water may also be present in the crystal lattice. Particle size is controlled in the active substance specification to ensure the performance of the finished product.

Manufacture, characterisation and process controls

Filgotinib maleate is synthesized convergently in several main steps using well-defined starting materials with acceptable specifications. The starting materials were discussed with CHMP during a scientific advice procedure and the applicant followed the advice.

The Applicant has presented a comprehensive understanding of the origin, fate and purge of impurities generated during each step supported by spiking experiments at appropriate levels. In-process controls (IPCs) are in place to monitor key impurities. The final crystallisation and isolation step has been designed to control the polymorphic form and particle size distribution of filgotinib maleate.

An enhanced development approach was used for the design of the active substance manufacturing process using elements of the Quality by Design (QbD) paradigm. For each step, a D-Optimal DoE (Design of Experiments) study was performed at lab scale. The selection of the factors included in each DoE study and their ranges was guided by risk assessment (FMEA) informed by reaction understanding, prior knowledge, and univariate experiments. The responses for each DoE were appropriate and included the levels of the main impurities requiring control. Acceptance criteria for the selected responses are the same as those listed in the intermediate and active substance specifications.

For each DoE, statistical models were generated for the laboratory scale experiments and assessed using a defined process described for each response.

A design space is claimed for all the steps of the manufacturing process. Each design space is clearly described with parameter ranges defined in tabular format within the process description. The experiments to define the design spaces were conducted on lab scale although indications from further process development work are that there is no scale and equipment size dependency. However, a design space verification protocol has been submitted to cover commercial scale processing and is deemed acceptable.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The manufacturing route to filgotinib has been essentially the same throughout development. The applicant has demonstrated that the process parameters in place are sufficient to ensure the correct polymorphic form is generated. The active substance impurity profile has been similar throughout development.

The active substance is packaged in sealed double polyethylene bags stored in heat sealed, polyethylene-lined aluminium foil pouches. The foil bags are held in high-density polyethylene drums. The primary packaging material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), insoluble particulates (visual inspection), water content (Ph. Eur.), maleic acid content (HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), volatile organic impurities (GC) and particle size (laser diffraction).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. A risk assessment was conducted for the presence of potentially mutagenic impurities in the active substance and those identified were then assessed by QSAR analysis. If a risk wasn't ruled out, then Ames testing was conducted. 2 compounds were identified which are classed at class 2 and 3 according to ICH M7 respectively. Spike and purge studies were conducted to evaluate amounts present in the active substance relative to the TTC for each impurity. It was demonstrated that controlling these impurities according to ICH M7 option 3 (as unspecified impurities in either a starting material or intermediate) ensures that they are purged well below the respective TTCs.

Adequate justification was provided for omitting some tests from the specification. Process parameters have been shown to control polymorphic form so no test is required. The active substance has a low water activity so a test for microbial examination is not necessary. Risk assessments have concluded that no control of elemental or inorganic impurities are needed.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from pilot and production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 4 pilot and production scale batches of active substance covering both of the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 18 months under long term conditions (30ºC / 75% RH) and for up to 6 months under accelerated

conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance; assay; impurities; water content. The analytical methods used were the same as for release and were stability indicating.

No significant changes to appearance, assay or impurity content were observed. There was a small initial increase in water content which stabilised after 3 months without further trends. In addition, supportive data was provided to demonstrate that particle size, polymorphic form and maleic acid content do not change over time.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. Filgotinib maleate is not photosensitive. Samples were also stored at either -20 or 60ºC for up to 4 weeks. Other than an initial increase in water content, no other changes were observed. Filgotinib was found to be degraded by hydrogen peroxide, light, acid and base when in aqueous solution.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months stored below 30 ºC in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as film-coated, immediate release tablets in two strengths (100 mg and 200 mg). The 100 mg tablets are beige, capsule-shaped and debossed with GSI on one side and 100 on the other. The 200 mg tablets are beige, capsule-shaped and debossed with GSI on one side and 200 on the other. The tablets can be distinguished by size, debossing and packaging and are intended for different patient populations.

Component
Filgotinib Drug Substance
Microcrystalline Cellulose
Lactose Monohydrate
Pregelatinized Starch
Colloidal Silicon Dioxide
Fumaric Acid
Magnesium Stearate
Film-Coat
Opadry II Beige 85F97282
Purified Water

The aim of development was an immediate release solid oral dosage form. In phase 1, 2 and 3 clinical studies, different formulations were used for practical reasons. Pharmacokinetic studies demonstrated that the profiles of the various formulations are equivalent *in vivo*.

Filgotinib maleate is a crystalline solid with a single known polymorph which is stable during formulation. It exhibits pH-dependent solubility. It is classed as Biopharmaceutics classification system (BCS II), i.e. low solubility but high permeability. In order to prevent degradation, a desiccant is included in the primary packaging.

The chosen excipients are controlled according to Ph. Eur. standards, except for the film-coating for which there is an in-house standard. However, the coating components are of Ph. Eur. standard. No novel excipients are used and no incompatibilities were identified between filgotinib maleate and the excipients. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Initially, there was very little information on the development of the dissolution method, although the applicant had sought scientific advice on the topic on several occasions. The CHMP advice had not been clearly addressed in the description of how the dissolution method was developed and the discriminatory ability of the dissolution method had not been satisfactorily demonstrated. Questions were raised, both as major objections and other concerns. In response, the applicant further explained the development of the method and the investigation of its discriminatory power. Comparative dissolution profiles were provided for both tablet strengths. The QC dissolution method uses the paddle apparatus. The justification was deemed acceptable and the method is suitable as a QC procedure.

Taking into account the properties of the active substance, a granulation approach was adopted, followed by compression to form tablets and then film-coating. Some elements of a QbD approach were applied. Risk assessments were carried out, informed by prior knowledge to identify potential critical process parameters (CPPs) for each step that could have an impact on finished product critical quality attributes (CQAs). These parameters were then investigated using both univariate and multivariate experimentation and optimised accordingly. For the roller compaction step, a full factorial DoE was carried out. The properties of the resultant powder blends were then measure, as well as the properties of the tablet cores following compaction and the film-coated tablets. All materials met with their acceptance criteria, irrespective of the DoE input parameters. Nonetheless are considered CPPs for the commercial granulation process. The applicant has declared that no design space is claimed and that parameters will be at their set-points. Only 1 parameter at a time may be moved from its set-point within the proven acceptable ranges (PARs).

Tablets are packaged in HDPE bottles, fitted with screw caps and sealed with an aluminium liner prior to first opening. Each bottle also contains a sachet of desiccant (silica gel) to control moisture exposure and a polyester coil. Regarding the material in bottles and screw caps, compliance with relevant EU regulations and Ph. Eur. quality requirements are declared.

The primary packaging is an HDPE bottle, fitted with a screw cap and sealed with an aluminium liner prior to first opening. Each bottle also contains a sachet of desiccant (silica gel) to control moisture exposure and a polyester coil. The material primary materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of several main steps. The process is considered to be a standard manufacturing process.

There are several process intermediates. Data has been provided to justify the bulk holding times for each intermediate.

Manufacture of multiple batches up to double the planned commercial scale during development batches has demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Formal process validation will be carried out on 3 production scale batches of each strength of tablet prior to commercialization. The process validation plan is deemed adequate. The IPCs are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identity (HPLC, UV), water content (Ph. Eur.), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph Eur.), dissolution (Ph. Eur.) and microbiological examination (Ph. Eur.).

The proposed array of tests is deemed to be acceptable. The degradation product limit is justified.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. No risk was identified. In addition, batch analysis data on several pilot to production scale batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it is not necessary to include any elemental impurity controls in the finished product specification.

The applicant submitted a risk evaluation on the potential presence of nitrosamines in Jyseleca. Both active substance and finished product manufacturing processes were considered, along with raw materials and packaging. No significant risk was identified. The analysis was deemed acceptable.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for several pilot to production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released onto the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 4 pilot to production scale batches of each strength tablet stored for up to 18 months under long term conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of Jyseleca were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, assay, degradation products, water content, dissolution and microbiological examination. The analytical procedures used are stability indicating.

No significant changes to any of the measured parameters were observed, other than a small decrease in water attributed to the presence of the silica desiccant.

An in-use study was performed on 1 batch of each strength for 30 days. At the end of the period, water content had increased otherwise the results are in line with those of the other stability studies. Considering the specification limit set for water, the commercial pack size is 30 tablets/bottle and the intended dosage regimen is one tablet once daily, the results do not cause concern.

In addition, 1 batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not photosensitive. Samples of both strengths were also stored at 60°C for 2 weeks and -20°C for one month without negative impact on the evaluated parameters.

Based on available stability data, the proposed shelf-life of 24 months with the following storage statement as stated in the SmPC (section 6.3) is acceptable: "This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture. Keep the bottle tightly closed."

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing processes. Design spaces have been proposed for all steps of the active substance manufacturing process but not for the finished product. An adequate design space verification protocol has been provided.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary pharmacodynamic studies

In vitro – biochemical assays

Filgotinib has been tested in different biochemical kinase assays against the JAK family members (JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2)). The *in vitro* enzymatic activity of human JAKs were measured by 33P-incorporation analysis, TriFRET and ULight assays. In these assays, filgotinib repetitively inhibited JAK1 and JAK2 with similar potency; half max inhibitory concentration (IC50) of 10-53 nM and 28-29 nM, respectively. For JAK3 and TYK2 family kinases 6- to 80-fold (311-810 nM) and 3- to 11-fold (116-177 nM) higher IC50 values, respectively, were observed. Even though, filgotinib exerts lower inhibitory activity against JAK3 and TYK2, the IC50 values are well within clinically relevant concentrations (Cmax~6 µM).

Also, the main metabolite GS-829845 was assessed regarding its capacity to inhibit the different human JAKs. The metabolite shows 10-fold lower potency against JAK1 and JAK2 than filgotinib itself (IC50 around 500-600 nM). The exposure of the GS-829845 metabolite at steady state, Cmax 9.8 µM, suggests that this major metabolite may contribute to JAK1 and JAK2 inhibitory effects *in vivo*. The metabolite

displayed > 5-fold selectivity for JAK1/JAK2 over JAK3/TYK. The IC50 values for JAK3 and TYK2 were >3606 and >2996 nM, respectively, indicating that this main filgotinib metabolite GC-829845 may also contribute to JAK3 and TYK2 inhibition *in vivo* at higher doses.

Notably, all the biochemical assays were conducted in the presence of adenosine triphosphate (ATP) concentrations ≤10 µM. In Clark et al, filgotinib were tested in biochemical assays in the presence of 1000 µM ATP. As expected, higher IC50 values for all JAKs were seen. Filgotinib show IC50 values for JAK1 (363 nM), JAK2 (2400 nM), and JAK3(2600 nM) within concentrations of clinical relevance, whereas for TYK2 an IC50 > 10.000 nM were reported. The results confirm that several JAKs can potentially be targeted at clinical exposure levels.

In vitro cellular assays

Effects and cellular potency of filgotinib on JAK inhibition was studied in several different cell systems. The cell-lines used were all of human origin and treated with different stimuli known to phosphorylate particular STATs via different JAKs. For the JAK1 and JAK3 mediated phosphorylation of signal transducers and activators of transcription 6 (STAT6), STAT5 and STAT1 following interleukin-4 (IL-4), IL-2 and interferon γ (IFNγ) stimulations, IC50 values of 179 – 3364 nM were observed. None of these JAK dependent cell assays were specific for JAK3 and hence the relative contribution of JAK3 vs JAK1 in the JAK1/JAK3 dependent assay could not be discerned. The inhibition of STAT5 phosphorylation was studied in IL-3 and erythropoietin (EPO) induced TF1 cells and UT-7-EPO cells, both specific for JAK2 inhibition. The stimulation with IL-3 shows an IC50 of 3524 nM, whereas JAK2 mediated phosphorylation of STAT5 showed IC50 of >10.000 nM in the EPO induced cells.

It is difficult to draw any firm conclusions on potency and selectivity on specific JAKs from all cell assays conducted, but it can be concluded that filgotinib shows similar activity on JAK1 and JAK2 with IC50 values in the range of the concentrations found at steady state in RA patients, and potentially both these pathways are inhibited *in vivo*. The exception includes EPO stimulation of UT-7 cells where IC50 of > 10.000 nM were observed. However, the clinical relevance of this finding does not corroborate with toxicity findings in animal models. In rats and dogs, anaemia (an effect associated with EPO induced JAK 2 inhibition) was observed at 100 mg/kg (~10-fold exposure margin) and 5 mg/kg (~2-fold exposure margin), respectively. However, anaemia was not observed in the clinic.

In Oncostatin M (OSM) stimulated HeLA cells, filgotinib and the metabolite GS-829845 were studied against STAT1 phosphorylation (JAK1/JAK2 dependent) in a luciferase assay. The results show that the metabolite is around 10 times less potent than filgotinib itself, which is in agreement with biochemical studies.

In vitro blood cells (ex-vivo) studies

In the whole blood assays, blood was drawn from healthy subjects and pre-incubated *in vitro* with filgotinib and treated with different cytokines. The JAK-activities were quantified by measuring phosphorylation of STATs by flow cytometry or Enzyme linked immunosorbent assay (ELISA). In the signalling where JAK1 are involved, the STAT-phosphorylation was inhibited with IC50 values varying between 629-1789 nM; whereas the JAK2 dependent GM–CSF stimulated STAT5 phosphorylation was inhibited at higher concentrations (IC50 17453 nM). Filgotinib inhibited IL-6 induced STAT1 phosphorylation (JAK1/JAK3/TYK2 dependent signal) with IC50 values ranging from 629 nM to 1180 nM. Filgotinib also inhibited IL-2 induced STAT5 (JAK1/JAK3), IFNα STAT1 (JAK1/TYK2) and IL-6 STAT3 (JAK1/JAK3/TYK2) signalling with IC50 values between 1127-3410 nM. Since no JAK3 selective assay is available, it could not be sorted out from the JAK1/JAK3 dependent assays whether filgotinib is active on JAK1 only or both JAK1 and JAK3.

In study 185, filgotinib was studied in order to further assess the JAK1 over JAK2 selectivity. In the JAK2 inhibition of STAT5 by filgotinib in GM-CSF stimulated human blood cells, a 28-fold greater inhibition of JAK1 than JAK2 was found. The selectivity towards JAK1 over JAK2 with the experimental settings employed in above study is noted. In contrast, the *in vitro* selectivity assays have demonstrated that filgotinib shows similar activity towards JAK1 and JAK2 and furthermore somehow lower activity to JAK3 and TYK2 (but still at concentrations of clinical relevance). Moreover, inhibition of these JAKs could potentially be of clinical concern since both JAK2 and JAK3 associated effects have been observed in the animal toxicity studies. However, this was not clearly observed in RA-patients.

In study 186, the main metabolite GS-829845 was studied in whole blood, using same stimuli as in the filgotinib study 185. For the metabolite GS-829845, around 10-20-fold lower IC50 values were found for the different JAK1 specific pathways as compared to filgotinib itself. This is in agreement with the biochemical assays. Considering that the exposure of this metabolite is 16-21-fold higher than filgotinib after 200 mg twice a day (bid), the metabolite may exert PD effects that is of clinical relevance.

Species comparison

In addition to JAK inhibitory effects in humans, filgotinib blocked IL6 induced STAT1 and STAT3 phosphorylation in whole blood from rat and mouse indicating species cross-reactivity. The rat IC50 values are in same range as human IC50, whereas for mouse 3-fold higher IC50 values for filgotinib were observed. For the other species used in the toxicity studies (dogs and rabbits), no data regarding JAK-inhibition was presented. The applicant´s justification for this is based on the high sequence homology of the JAK family between species, data from other JAK-inhibitors that indicates similar inhibitory response between species and that dogs and rabbits has been considered as relevant species with these other JAK-inhibitors. Nevertheless, the CHMP reminded the Applicant that cross-reactivity data from all species considered for the toxicity testing is expected before actual inclusion in toxicology studies. However, this issue was no longer pursued by the CHMP.

In vitro comparison with other JAK inhibitors

Filgotinib was compared with other RA associated JAK inhibitors as baricitinib, tofacitinib, and upadacitinib. Baricitinib, tofacitinib and upadacitinib are potent inhibitors of pSTAT1 and pSTAT3 in humans with >10-fold lower IC50 values than filgotinib and 100-fold lower than the filgotinib metabolite in biochemical assays. This corroborate with the clinical situation, e.g. that the Cmax at steady state for filgotinib (2.6 µg/mL) is approximately 60-times higher than for upadacitinib (~40 ng/mL, Klunder B, 2019).

In vivo studies

In vivo collagen induced arthritis (CIA) rats, a common animal model for RA, were repeatedly used in a total of 12 PD studies. The rationale for conducting all these animal trials with overlapping dose administrations (doses ranges from 0.1 to 30 mg/kg/day) and readouts (clinical score, paw swelling, Larsen score) is not clear for the CHMP. Nevertheless, from the studies performed in male dark agouti (DA) rats it was demonstrated that two weeks treatment resulted in improvements of clinical score at lowest dose tested (0.1 mg/kg). Paw swelling was improved after 0.1 mg/kg (study 48) and after 0.3 mg/kg (study 53). For Larsen score improvement, higher doses were required; in study 46 and 48 the highest doses of 20 mg/kg and 10 mg/kg, respectively did not result in any improvement of Larsen score, whereas in study 53, 3 mg/kg was associated with a significant effect. In study 51, additional histopathology parameters including pannus severity, cell infiltration, cartilage and bone lesions were studied at doses between 0.3-30 mg/kg. At 10 mg/kg a decrease in pannus severity was found, whereas

for the other cartilage and bone sparing parameters studied, no significant improvements were observed at the highest dose tested 30 mg/kg.

From the *in vivo* CIA studies in DA rats, it can be concluded that for cartilage and bone effects, higher doses of filgotinib is needed than for the anti-swelling and clinical effects. Exposure of filgotinib in CIA DA rats (as analysed in study 53) revealed that the effective dose of 0.3 mg/kg corresponds to Cmax of 19 ng/ml whereas 3 mg/kg corresponds to Cmax of 363 ng/m. Hence, both the anti-swelling effects and improvement in bone markers are seen at concentrations of clinical relevance.

Lewis female CIA rats were dosed with 1-10 mg/kg and ankle swelling was improved in the 5 mg/kg bid treatment (but not at 10 mg once daily (QD)). The reason for the female CIA rats requiring higher doses for anti-swelling effect is not clear and has not been discussed by the Applicant. However, since no gender differences have been noted in the human subgroup analyses (assessed as endpoint ACR 20) of trials FINCH 1, 2 and 3 (see the clinical section 2.5) this PD and PK differences between CIA models were not considered to be of any clinical relevance to the CHMP. Notably, in the PD study in Lewis rats (PC-417-2010, 2019), high concentrations corresponding to the intended therapeutic exposure were tested but with filgotinib failing to demonstrate any targeted activity. Moreover, similar negative results were obtained in PD combination studies, when filgotinib was administrated alone. The Applicant's explanation was that co administration of filgotinib with GS 829845 is necessary to achieve efficacy in PD model, which is agreed by the CHMP.

Efficacy of the combination was evaluated in 3 different studies (in the rat CIA model) with filgotinib and GS-829845 administered at different ratio administrated for 2 weeks. Two studies (0148 and 158) were performed with three different treatment groups: filgotinib administrated alone, GS-829845 administrated alone and treatment with the combination. The third study was performed only with the combination (ratio 1/20) at different doses; in this recent third study (PC-417-2006, 2019), administration of combination filgotinib/GS-829845 showed significant dose-dependent efficacy at exposure approximately similar to the human therapeutic exposure. In the two earlier studies (0148 and 158, 2011 and 2012) the effect of filgotinib on GS-829845 activity (and vice versa) have been studied. Controversial results were obtained: in study 158, additive activity was observed when the compounds were administered in combination compared to each compound administered alone at the same doses, whereas in study 0148, filgotinib antagonised GS-829845 activity when administered in combination. In this second study, it was necessary to increase GS-829845 proportion in the ratio to retrieve a PD effect. The applicant concluded that the evaluation of filgotinib and GS 829845 co-dosing in rat CIA studies showed additive, and not antagonistic, effects of filgotinib and GS 829845 at reducing PD (pSTAT1) and demonstrating efficacy in the rat CIA. However, in study 0148, the combination of filgotinib/GS-829845 at low doses (3/30 mg/kg, respectively) was less effective on all measured parameters (clinical score, change of paw swelling and global Larsen score) than filgotinib (3mg/kg) or GS-829845 administered alone (30 mg/kg). On the contrary, when the combination filgotinib/GS-829845 was administered at 6/60 mg/kg an additive effect was observed. In addition, in the more recent study PC-417-2006, when the combination filgotinib/GS-829845 was administered at ratio 1/20 and in clinical therapeutic range, low additive effects were observed but the overall PD effect was mostly driven (>90%) by the metabolite GS-829845. This is reflected in section 5.1 of the SmPC.

Secondary pharmacodynamic studies

In vitro binding screening and kinase activity profiling were performed in several studies including over 450 protein kinases, 70 receptors and 22 enzymes. Some kinases displayed IC50 values below the Cmax for filgotinib. For some kinase targets competitive inhibition >50 % of ATP binding was observed, e.g. 95 % inhibition for Liver Kinase B1 (LKB1)and73 % inhibition for Serine/Threonine Protein Kinase 1 (SRPK1).

The Applicant argues that due to higher potency towards JAK1 than to these non-JAK kinases, no meaningful impact from these targets are expected.

The GS-829845 metabolite appears to be more promiscuous than filgotinib itself, binding to around 20 non-JAK associated kinases in off-target binding assays. When enzymatic inhibition study was conducted, two non-JAK kinases were identified, i.e. Aurora B Kinase (AURB) (IC50 1.5 µM) and FMS (IC50 3.6 µM). Two follow up cell assays were conducted with AURB (a kinase involved in cell cycle regulation) concluding that AURB was not inhibited when concentration up to 10 µM filgotinib were tested. Surprisingly GS-829845 was not tested in any of these experiments and hence it cannot be concluded if GS-829845 possesses any AURB off-target effects at clinically relevant concentrations. Nevertheless, as the toxicity studies have not identified any specific GS-829845 related concerns, off-target binding by GS-829845 is most likely not of clinical relevance.

Safety pharmacology programme

In the safety pharmacology studies, filgotinib and GS-829845 had no effect on the central nervous system and respiratory system in rats at doses up to 180 mg/kg. The dose of 180 mg/kg corresponds to concentrations >10.3 ug/mL and > 29 ug/mL (no PK data provided 180 mg/kg), resulting in exposure margins above 10-fold and 8-fold, respectively. In the *in vitro* human ERG assay, low liability for delayed rectifier potassium current (Ikr) inhibition was seen with both filgotinib and GS-829845 at the lowest dose tested (10 uM). This corresponds to exposure margin of around 2-fold for both filgotinib and GS-829845. No QTc effects were observed in the dogs with highest dose tested which corresponds to exposure margin around 2.5 - 7-fold for filgotinib and GS-829845 metabolite, respectively. However, in clinical studies a minor QT prolongation (<10 msec) have been observed at supra-physiological doses that was considered of no clinical concern.

In the cardiovascular (CV) studies in dogs, oral administration of filgotinib did not impact on any CV parameters. The metabolite GS-829845 on the other hand, increased heart rate (HR) (+41-52 bpm) and decreased blood pressure (BP) (up to 25 mmHg) at 100 mg/kg. The No Observed Adverse Effect Level (NOAEL) (25 mg/kg) corresponds to exposure margins of 7 (based on Cmax). The clinical relevance of GC-829845 induced increase in HR and decrease BP in dogs is probably low, since this have not been reported as a concern in the toxicity studies or the human clinical trial TOT-study, where supra-physiological doses of filgotinib were administered.

Pharmacodynamic drug interactions

No formal drug interaction study was conducted in animals which was considered acceptable to the CHMP.

2.3.2. Pharmacokinetics

The non-clinical PK of filgotinib was evaluated in a series of *in vitro* and *in vivo* studies conducted in mice, rats, dogs, minipigs, rabbits, cynomolgus monkeys.

The absorption of filgotinib was studied *in vitro* in Caco-2 cells and *in vivo* after single dosing to rats, mouse, dog, rabbit, minipigs, and cynomolgus monkeys. Filgotinib's transepithelial permeability was high, and filgotinib was rapidly absorbed in all species tested. The clearance was low and distribution volumes greater than total body water in all species with T1/2 times between 4-10 hours.

Binding to plasma proteins of filgotinib and the GS-829845 metabolite were low (25-70%) in all species studied, including humans. In human hepatic microsomes a free fraction of 86% and 95% were observed. In tissue distribution studies in rats with radiolabelled filgotinib, the highest radioactive concentrations

were detected in uveal tract and urinary bladder. Of note; after 48 hours, filgotinib was retained in epididymis. No placental transfers or milk excretion studies were conducted.

The *in vitro* studies indicate that the main metabolite GS-829845 is formed by first passage metabolism predominantly by CES2. In humans, the exposure (AUC) of GS-829845 are 16-21 fold higher than the AUC for filgotinib. Neither of the species used in non-clinical studies show the same exposure ratios (highest AUC ratio of 1.57 was found in mice). Consequently, the GS-829845 needed to be separately studied and accordingly the Applicant has conducted repeat toxicity, genotoxicity, repro toxicity and cancer studies with this metabolite. It is estimated that around 20% of administered filgotinib is metabolized to cyclopropane carboxylic (CPCA)-carnitine. Mouse and dog appear to be the nonclinical species that are adequality exposed for this metabolite.

The studies indicate that faecal elimination is the dominant route (59%) in dog, whereas in rat, urinary excretion is more common (59%). In humans, 87% of administered dose of radioactively labelled compound was excreted in urine and 15% in feces.

The toxicological profile of filgotinib has been evaluated in non-clinical studies in agreement with relevant guidelines. In addition, the major human metabolite GS-829845, which in animal species is formed following dosing of filgotinib, was also assessed as multiples of the observed human GS-829845 exposure could only be achieved after co-dosing or administration of GS-829845 alone. In human whole blood assays, GS-829845 is approximately 10-fold less active than filgotinib, while having a similar JAK-1 selectivity profile. Overall, the toxicity profile of filgotinib (and GS-829845) has been characterized via repeat dose toxicity (up to 1 month in CB6F1-nonTgrasH2mice, 6 months in Sprague Dawley rats and 9 months in beagle dogs), genotoxicity (filgotinib only), carcinogenicity studies in Sprague Dawley rats (2 years study) and CB6F1-TgrasH2 mice (6 months study), reproductive and developmental toxicity studies in Sprague Dawley rats and New Zealand White rabbits, juvenile toxicity, *in vitro* and *in vivo* genotoxicity, local tolerance, and phototoxicity studies.

The oral route of administration was utilized in all toxicity studies to match the intended clinical administration route.

2.3.3. Toxicology

Table 1 Overview of conducted toxicological studies

Study type and duration	Test article	Route of administration	Species	GLP
Single–dose toxicity	Filgotinib	Oral	Dog	No
Repeat-dose toxicity				
3 days (phase 1) 14 days (phase 2)	Filgotinib and GS-829845	Oral	Dog	No
1 week	Filgotinib and GS-829845	Oral	Mouse, Rat, Rabbit	No
2 weeks	Filgotinib and GS-829845	Oral	Rat, Dog	No
4 weeks	Filgotinib and GS-829845	Oral	Mouse, Rat, Dog	Yes
13weeks	Filgotinib and GS-829845	Oral	Rat, Dog	Yes
26 weeks	Filgotinib and GS-829845	Oral	Rat, Dog	Yes
39 weeks	Filgotinib and GS-829845	Oral	Dog	Yes
Genotoxicity				
In vitro reverse assay	Filgotinib	*In vitro*	Bacteria	Yes
In vitro mouse lymphoma assay	Filgotinib	*In vitro*	Mouse lymphoma cells	Yes
In vivo micronucleus test	Filgotinib	Oral	Rat	Yes

Carcinogenicity				
26 weeks	Filgotinib and GS-829845	Oral	C6BF-1 TgrasH2 mouse	Yes
104 weeks	Filgotinib and GS-829845	Oral	Rat	Yes
Reproductive and developmental toxicity				
FEED	Filgotinib and GS-829845	Oral	Rat	Yes
EFD	Filgotinib and GS-829845	Oral	Rat, rabbit	Yes (DRF, No)
PPND study	Filgotinib and GS-829845	Oral	Rat	Yes
Juvenile toxicology	Filgotinib and GS-829845	Oral	Rat	Yes
Local tolerance				
Dermal irritation	Filgotinib	*In vitro*	Mouse, human	Yes
Ocular irritation	Filgotinib	*In vitro*	Cow	Yes
Phototoxicity	Filgotinib	*In vitro*, oral	Mouse, rat	Yes
Other Toxicity Studies				
Mechanistic study	Filgotinib	Oral	Rat	no
In vitro reverse assay	GS-829845	*In vitro*	Bacteria	Yes
In vitro mouse lymphoma assay	GS-829845	*In vitro*	Mouse lymphoma cells	Yes
In vivo micronucleus test	GS-829845	Oral	Rat	Yes
Repeat-dose, 4-weeks	GS-829845	Oral	Rat	Yes/no
Repeat-dose, 26-weeks	GS-829845	Oral	Dog	Yes
Photoxicity (neutral red uptake)	GS-829845	Topical	Mouse fibroblasts	Yes
Impurity qualification, 4-week	Filgotinib		Rat	Yes
DRF, 7-days	GS-830681	Oral	Rat	Yes
Genotoxicity, 28-days (incl. Pig-a analysis with comet)	GS-830681	Oral	Rat	Yes
Impurity/Bacterial mutation	G499768, G499772, G016271, G016943, G163448 , G230415 and 3,5 difluorop henyl boronic acid	*In vitro*	Bacteria	No
Impurity/Bacterial mutation	G160462, G016612, G017262, G502229, G502234, G940758, di-urea, G062152, A-51352, A-1648398.0	*In vitro*	Bacteria	Yes
Combination toxicity, 14 days	Filgotinib and GS-829845 or Filgotinib and GS-829845	Oral	Dog	No

Relevance of animal models

The Sprague Dawley rat and Beagle dog were selected as the main rodent and non-rodent species in the general toxicity studies. The Sprague Dawley rat and the CB6F1-TgrasH2 mouse were selected for the carcinogenicity studies and reproductive studies were conducted in Sprague Dawley rat and New Zeeland White rabbits.

As discussed in the pharmacological section, data on JAK inhibitory effects in mice and rats have indicated that there is a cross-reactivity in these species which could qualify them as relevant toxicological species. No such data has been presented for dogs and rabbits.

Single dose toxicity

Single dose toxicity was tested in dogs and was conducted as the first part of a two-part study. Animals were dosed up to 100mg/kg/day. No lethality was identified. Clinical signs as vomiting (vehicle 1 and 3) and hypersalivation (vehicle 2) was observed at the highest dose.

Repeat dose toxicity

In all pivotal repeat-dose toxicity studies, except for rat 4-week study, animals were administered with filgotinib or with the metabolite GS-829845 alone. The main organs and tissues affected were primarily male reproductive organs (testes and epididymides) and lymphoid organs and tissues.

Mortality

In the non-pivotal 7-day study in mice the highest dose (500 mg/kg/day) were tolerated. In the subsequent pivotal 4-week mice study doses of 50, 500 and 1500 mg/kg/day were selected. Two mortalities considered to be related to filgotinib occurred in the high dose group, one animal died on day 3 and with clinical signs of poor condition on day 1-3 in all remaining high dose animals, the dose was thereafter reduced to 1000 mg/kg. At this dose the second mortality occurred on day 26. However, exposure measured on day 28 (3 days with 1500 mg/kg followed by 1000 mg/kg for 25 days) were several multiples (AUC 27-44 times; Cmax 23-times) compared to the clinical dose at 200 mg/kg/day. No mortalities occurred at doses up to 1500 mg/kg/day with GS-829845.
No test-article related deaths occurred in rats.
In dogs no test-article related deaths occurred in the 13-week study. In the longer 26 and 39-week studies mid and/or high doses were adjusted due to unexpected clinical signs and premature sacrifice. The applicant considered these deaths related to misdosing/aspiration of compound in lungs. With the new dose settings one female dosed with 10 mg/kg/day of filgotinib were prematurely sacrificed due too poor clinical condition considered related to filgotinib. Among other findings, pronounced lesions in the buccal cavity and gastrointestinal tract lymphoid atrophy was observed in the thymus, spleen, GALT and mesenteric lymph node. The dose of filgotinib at 10 mg/kg/day corresponded to a 7.8-fold AUC exposure compared to a clinical dose or 200 mg.

Male reproductive organs

Male reproductive organs were affected after administration of filgotinib in all toxicological species. No corresponding effects were observed after administration of the metabolite GS-829845 alone in rats and dogs, except in the pivotal 13-week dog study at doses ≥ 20 mg/kg/day. In mice effects were observed only in single animals at high dose with GS-829845. The effects appeared at different exposure levels across the species with dog being most sensitive. In dogs, effects were observed already after 4-weeks of administration while in rat effects were seen after 13 weeks. In rats and dogs, there were no profound changes of the findings with longer duration of administration. The observed lesions consisted of germ cell depletion/degeneration and/or tubular vacuolation in testis with correlating findings in epididymides (reduced sperm content and/or increased cell debris). In the 4-week mice study, adverse effect was observed from 500 mg/kg/day, however effects were also observed at 150 mg/kg/day consisting of minimal to moderate testicular atrophy/degeneration with minimal to slight sloughed cells in the epididymides, but these findings were not considered as adverse effects by the applicant. The findings in

male reproductive organs was the most profound lesions for the NOAEL setting. In male rats, findings of up to marked/severe grade in testis and epididymides was observed from a dose of 45 kg/mg/day in the 26-week study and the NOAEL was set to 20 mg/kg/day which corresponds to 2.3-fold marginal to the clinical AUC exposure at 200 mg. In dogs, corresponding adverse effects were observed from 5 mg/kg/day in the 26-week study and at 10 mg/kg/day in the 39-week study. There was no or very low (0.9 and 1.7-fold) AUC exposure marginals at NOAEL compared to the clinical exposure at 200 mg in dogs after 26 and 39 weeks of administration, respectively.

At LOAEL for male reproductive organs generally no changes of hormonal levels or seminology parameters was observed except for increased luteinizing hormone (LH) levels in rats. At higher doses (and exposure) a decrease of testosterone, follicle-stimulating hormone (FSH) and inhibin levels was observed in rats. In dogs, no changes of testosterone or FSH levels were observed at any dose.

A recovery group was included in the 13-week study in rats which showed persisting findings in testes (minimal to moderate) and epididymides (minimal to severe) after 8 weeks of recovery when dosed at 180 mg/kg/day (only high dose animals were included). In dogs treated for 13-weeks and after 8 weeks of recovery a reduced sperm counts, and number of normal sperms persisted without microscopic findings in testes or epididymides. No recovery groups were included in longer-term rat and dog repeat dose toxicity studies which would have been beneficial to better characterize potential reversibility of observed toxicity.

In the male fertility study in rat, comparable changes of male reproductive organ as described above occurred after administration with filgotinib.

The applicant has conducted a mechanistic study in rats to investigate testicular toxicity including a genomic analysis. According to the applicant, filgotinib did not affect the transcription of genes relevant to the JAK pathway in testis and the gene expression observed did not match any profile published or within public database and suggests that the testicular toxicity represent a novel mechanism.

Immune system

Effects consistent with the inhibition of JAK1/3 were observed in nearly all dose levels in repeated dose toxicity studies of all species assessed after administration of either filgotinib or GS-829845. These effects included decreases in circulating lymphocytes (T-cells; total, helper and cytotoxic) and natural killer (NK) cells, and decreased cellularity and/or lymphoid depletion in lymphoid tissues.

In rats at filgotinib doses from 100 mg/kg adverse effects was observed with up to frequent and severe effects on multiple lymphoid tissues and a 70-75% decrease of circulating lymphocytes. In dogs, the effects on lymphoid tissues and circulating lymphocytes appeared milder. The NOAEL for JAK-1 related changes were with filgotinib 45 mg/kg/day in rat and 5 mg/kg/day in dogs corresponding to 6-fold and 1.8-fold, respectively, compared to the AUC clinical exposure at 200mg/kg.

Altered immune function-secondary effects

In dogs, the main manifestation of immunosuppression was the occurrence of infections. Demodex spp. is a mite considered to be normal flora of the dog skin which is otherwise controlled by the innate immune system. In the 39-week study, parasites consistent with Demodex spp. was confirmed in all high dose males and in 2/5 low dose males (2.5 mg/kg, clinical exposure) but associated macroscopic findings (cutaneous lesions recorded as increased size of erythema, desquamation, alopecia, thickening and swelling, and wounds and scabs) and marked granulomatous inflammation were observed only in high dose males.

Haematopoietic system

Decreases of red blood cell (RBC) parameters (red blood cell, haemoglobin and haematocrit) and reticulocytes which are effects consistent with JAK-2 inhibition were observed in mice, rats and dogs administrated with filgotinib but no obvious corresponding effects in animals administrated with GS-829845. In rats, reduced RBC parameters were observed at doses from 100 mg/kg/day and in dogs at 5 mg/kg/day with NOAEL at 45 mg/kg/day in rat and 2.5 mg/kg/day in dogs corresponding to 6-fold and 1.1-fold, respectively, compared to the AUC clinical exposure at 200mg/kg. However, no changes in prolactin levels were observed in rats.

Teeth

Filgotinib related effects on incisor teeth was observed in the 26-week rat study. At 45 mg/kg/day changes in the lower incisor tooth enamel, termed striae, was observed and at 100 mg/kg/day the changes included slight to marked degeneration/loss/disorganization of ameloblast accompanied with malformed enamel. The NOAEL for these findings was set to 20 mg/kg/day corresponding to 2.8-fold of the clinical AUC exposure at 200 mg/kg. No corresponding findings were observed in juvenile rats (up to postnatal day 183) dosed up to 20 mg/kg/day. Filgotinib related findings in incisor teeth was not observed in mice or dogs. The applicant considered these findings not relevant for humans due to that, unlike in man, rat incisors grow throughout their lives and are therefore continuously depositing new enamel while in humans enamel formation is complete once secondary dentition is finished, generally, in the late teens.

Repeat dose toxicity

Fertility and early embryonic development

Two separate studies were conducted to evaluate male and female fertility potential and embryonic development in rats after administration of filgotinib and the metabolite GS-829845. Profound effects were observed after administration with filgotinib but not with GS-829845.

In the first study using untreated males, females were treated with filgotinib at 15, 30 and 60mg/kg/day or with 60 and 180 mg/kg/day with GS-829845. Dosing of 60 mg/kg/day with filgotinib resulted with adverse effects on mean % post implantation loss which was due to an increase mean number of early and late resorptions. In the second study males were treated with filgotinib at 15, 30 and 60 mg/kg/day or with GS-829845 at 60 and 180 mg/kg/day. Severe effects on male fertility was observed at 60 mg/kg/day with up to marked changes in testis and epididymides, sperm quality and quantity and fertility index of 5% compared control animals (95%). Only one female that mated with males at this dose became pregnant. No toxicokinetic was performed which was acceptable to the CHMP. The NOAEL for filgotinib was set to 30 mg/kg/day which in the pivotal 13-week study corresponded to approximately a 3-fold AUC exposure marginal to the clinical daily dose at 200 mg.

Embryo-foetal development

Embryo-foetal development studies were conducted in rats and rabbits administrated with filgotinib or GS-829845. Rats were dosed with filgotinib at 25, 50 and 100 mg/kg or with GS-829845 at 60 and 180 mg/kg/day and rabbits were dosed with filgotinib at 10, 25 and 60 mg/kg or with GS-829845 at 60 and 150 mg/kg/day. Profound effects were observed in both species after administration with filgotinib or with GS-829845. In rats, increased post implantation loss and a decrease number of live foetuses and foetal body weight were observed at high filgotinib dose (100mg/kg). Visceral and/or skeletal abnormalities occurred at all doses with filgotinib and GS-829845. Dose-related increase in incidence of abnormalities

included, among others, vertebrate and sternal abnormalities, rudimentary ribs, dilated/convoluted ureter, internal hydrocephaly, and absent or small eyes. No NOAEL was established. The AUC exposure at the lowest dose corresponded to 2.4-fold (filgotinib) and 1.7-fold (GS-829845) to the clinical exposure at 200 mg. Similar effects was observed in rabbits including increased post implantation loss and a decrease number of live foetuses and foetal body weight at high doses and visceral and/or skeletal abnormalities at all dose levels. No NOAEL was established. The AUC exposure at the lowest dose corresponded to 1.4-fold (filgotinib) and 4.9-fold (GS-829845) to the clinical exposure at 200 mg.

Prenatal and postnatal development

The potential effects of filgotinib and GS-829845 on development, growth, behaviour, reproductive performance and fertility of F1 generation were evaluated in rats at doses of 2, 5 and 15 mg/kg/day (filgotinib) or 10 and 30 mg/kg/day (GS-829845). No adverse effects occurred at any dose in the study. The AUC exposure at the highest dose of filgotinib (15 mg/kg/day) and GS-829845 (30 mg/kg/day) corresponded to a 1.2-fold and 0.8-fold marginal, respectively, to the clinical dose at 200 mg/kg/day. It is considered that this study is not conclusive due to the low exposure of the animals.

Juvenile toxicity

The current application concerns an indication in for treatment in adults only, therefore juvenile toxicity studies are considered to be of low relevance for this application. However, in the pivotal juvenile toxicity study conducted in Sprague Dawley rats no adverse findings occurred at administrations up to 20 mg/kg/day (filgotinib) or 90 mg/kg/day (GS-829845) corresponding to 2.2-fold of the clinical AUC exposure at 200 mg/kg.

Genotoxicity

Filgotinib did not induce mutations when adequately tested in five histidine-requiring strains of Salmonella typhimurium (TA98, TA100, TA1535, TA1537 and TA102) at concentrations up to 5000 µg/plate in the absence and in the presence of a rat liver metabolic activation system (S9). In the *in vitro* mammalian chromosome aberration test in mouse lymphoma cells, filgotinib was negative at dose levels up to 500 µg/mL (signs of cytotoxicity were noted at levels of 5.1 µg/mL and above). In the two *in vivo* chromosomal aberration test (micronucleus) filgotinib was not clastogenic at doses up to 45 mg/kg or 1000 mg/kg. In the latter study the high mortality occurred at the high dose 2000 mg/kg and was not considered relevant by the applicant for micronucleus scoring.

Carcinogenicity

Long-term study

In the 2-year rat study the animals were dosed up to 45 mg/kg/day with filgotinib or with GS-829845 up to 75 mg/kg/day. The applicant selected the dose levels based on immunosuppression observed at higher doses in rats in previous studies and according to recommendations from Executive CAC. The exposure multiples for the maximum dose in male and female rats relative to the 200 mg clinical dose were 2.6 and 5-fold -fold for filgotinib and approximately 2-fold for GS-829845. Toxicity was observed from mid-dose with filgotinib and the exposure at the highest dose of the metabolite GS-829845 exceeded the clinical exposure at 200mg/kg. Therefore, the CHMP considered that the animals have been adequately exposed.

An increased incidence of Leydig cell adenoma was observed at 45 mg/kg filgotinib while no corresponding findings were observed with the metabolite GS-829845 (see Table 2). Other findings observed were similar to those observed in repeated toxicity studies including changes in male reproductive organs (testes and epididymides) at 45 mg/kg/day and lymphoid tissue at 15 mg/kg.

Table 2 Neo-plastic lesions

Lesion/organ		Filgotinib mg/kg/day			GS-829845 mg/kg/day	
	0	5	15	45	25	75
Leydig cell adenoma/ testes	3/90	2/60	1/60	9/60	4/70	3/70

The applicant considered the increased Leydig cell tumours to be related to a rat-specific mechanism involving increasing levels of LH that is linked to increase in rat Leydig cells tumours referring to Cook et al. 1999 and Chapin 2016 who further states that rat Leydig cells are considerably more sensitive to LH than human Leydig cells due to an increased number of LH receptors and an increased sensitivity. In the rat repeated toxicity studies filgotinib induced increased levels of LH (at 45 mg/kg daily dose for 39-weeks the LH levels increased with a 2-fold and dosing of 180 mg/kg increases were 6-fold compared to control animals) and Leydig cell hyperplasia at 60 mg/kg.

Short-term study

The 6 months study in mice resulted in no neo-plastic lesions after administration of filgotinib or the metabolite GS-829845. Non-neoplastic changes were seen in male reproductive organs after administration of filgotinib at 150 mg/kg/day similar to those observed in rat repeated toxicity studies at corresponding dosing although with milder grades of severity. Dose setting was based on immunosuppression observed at higher doses in the 4-week mouse study and according to recommendations from Executive CAC. The AUC exposure at the maximum doses tested relative to the 200 mg clinical dose was approximately a 6-fold for filgotinib and 8-fold for GS-829845. Toxicity was observed at high-dose with filgotinib and the exposure at the highest dose of the metabolite GS-829845 exceeded the clinical exposure at 200mg/kg. Therefore, the animals are considered being adequately exposed.

Toxicokinetics

Toxicokinetic assessment of filgotinib was included in all pivotal repeated-dose toxicology studies conducted in mice, rats and dogs after oral administration. In the rat 13 and 26-weeks studies and in all dog studies measurement of the human metabolite GS829845 after administration of filgotinib or with GS-829845 alone. Administration of GS-829845 alone was performed to reach multiples of exposure observed in humans. In mice, plasma exposures of filgotinib and GS-829845 were higher in males compared with female mice. The exposure proportionality varied between doses. In rats, filgotinib exposure increased 2-fold after 13 and 26 weeks in both genders as well as GS-829845 exposure after 26 weeks dosing with GS-829845. There were no significant differences between genders in rats.

Local Tolerance

Dermal and ocular irritation and testing has been made for filgotinib. By a mouse local lymph node assay and the Episkin reconstructed epidermis model, and by a bovine corneal opacity assay it was shown that filgotinib was not a skin irritating and non-corrosive and that filgotinib was a mild ocular irritant.

Other toxicity studies

Immunotoxicity

Specific immunotoxicity studies with filgotinib or GS-829845 was not performed. Considering the results in toxicological studies with decreases in white blood cells, T cells (total, helper and cytotoxic), and NK cells, decreased cellularity and/or lymphoid depletion in lymphoid tissues, and in one dog study an increased susceptibility to parasitic infection (Demodex spp.), it is clear that filgotinib and GS-829845 induces immune suppression. The CHMP considered that this is consistent with the action of mode and as such not unexpected.

Metabolites

The primary human metabolite GS-829845 has been evaluated in several non-clinical studies in parallel with filgotinib. GS-829845 standalone studies included mutagenic activity in bacterial reverse mutation testing, mouse lymphoma assay, bone marrow nucleus test, repeated toxicity studies in rat and dogs, and a photoxicity test with negative result. GS-829845 is considered to pose no risk for a genotoxic or phototoxic potential.

Impurities

An impurity qualification study has been conducted with filgotinib in rats for 4 weeks including two filgotinib lots***.*** No unexpected adverse effects were observed from filgotinib-related process impurities***.***

The Applicant investigated potential impurities. The Applicant performed directly in vivo genotoxicity studies on impurities GS 831208 and GS 830681. This strategy was based on literature references for in vitro results and the PigA and Comet assays selection.

Phototoxicity

In a 3T3 NRU mouse fibroblast assay it was shown that filgotinib was a potential phototoxic product with a Photo Impact Factor of 2.9 and Mean Photo Effect of 0.12. In a following *in vivo* phototoxicity study in Long Evans rats dosed with either filgotinib up to 180 mg/kg/day or GS-829845 up to 360 mg/kg/day for 3 days, no signs of phototoxicity was observed of either molecule. It can be concluded that filgotinib or GS-829845 pose no risk for phototoxicity.

Combination studies

Two combinations studies were performed with filgotinib/GS-829845 (ratio 1/6), one in rats and on in dogs with a 14-day treatment. The performance of these two studies was not justified or explained (selection of the duration or the doses). As there are pilot studies, it seems reasonable that the original plan was to perform longer studies. Moreover, filgotinib/GS-829845 ratio observed is human was 1/15 and not 1/6 as originally observed in phase I.

Regarding pilot study in dogs, no NOAEL could be established in view of immaturity of the male reproductive organs. Given the toxicity profile previously described, it is not acceptable and unnecessary that sexually immature dogs were used in this study and not in line with the 3Rs principles.

Regarding the pilot study in rats, filgotinib/GS-829845 was administrated for 14 days and the ratio filgotinib/GS-829845 was 1/6. Effects on lymphoid system and male reproductive system were observed

at all doses, these reproductive effects were considered adverse at mid- and high-dose (30/180 and 60/360 mg/kg/d) but not at low dose (10/60 mg/kg/d) given the low severity and the absence of correlating findings in epididymis. Therefore, the NOAEL was determined at this low dose, filgotinib/GS-829845 10/60 mg/kg/day. The Applicant stated that effects noted in the combination studies were comparable to those seen at similar exposures in individual repeat-dose studies of the two compounds. However, NOAEL determined for the combination (10/60 mg/kg/day) was lower than the NOAEL determined when filgotinib and GS-829845 were separately administrated (filgotinib 4-w study: NOAEL > 45 mg/kg/d, 13-w and 26w-studies: 20 mg/kg/day and GS-829845 no effect on male reproductive system up to 26 weeks, NOAEL > 180 mg/kg/day). Therefore, the absence of impact of the combination filgotinib/GS-829845 in terms of safety is questionable.

2.3.4. Ecotoxicity/environmental risk assessment

An ERA for the active substance filgotinib was performed in accordance with the CHMP guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr. 2).

The Phase I "worst case" PECsurfacewater of 1.28 µg/L increased to 2.12 µg/L following refinement based on prevalence data. The log Kow < 3 and filgotinib is not considered as a PBT or bioaccumulative substance.

A Phase II, Tier A assessment was provided. Filgotinib was not readily degraded and was found very persistent is sediment. Significant distribution to the sediment compartment was observed and a Phase II, Tier B assessment for sediment was provided. The Koc values below the limit of 1000 L/kg and a Phase II, Tier B terrestrial assessment is not required.

Studies on sewage microorganisms and freshwater aquatic organisms, representing three tropic levels have been performed using FIL DS, in accordance with current guidelines. No significant effects on the respiration of sewage sludge microorganisms, the early life stage of freshwater fish, or the growth of green freshwater algae, at their respective highest tested concentrations were observed. The no observed effect concentration (NOEC) for sewage sludge, freshwater green algae, and early life stages of freshwater fish were concluded to be ≥1000 mg·L-1, 5 mg·L-1, and 2.6 mg·L-1, respectively. The most sensitive taxonomic group tested was the freshwater invertebrate, Daphnia magna. Significant reduction in neonate production were observed at a FIL DS concentration of 2.6 mg·L-1. Based on this effect the NOEC was concluded to be 0.83 mg·L-1. In the sediment toxicity study in Chironomus riparius no effects on emergence ratio or development rates was observed and the NOEC was concluded to be 72.9 mg·kgdwt-1.

The calculated risk quotients were all below 1 and it can be concluded that no environmental effects are expected following the use of filgotinib.

Table 3 ***Summary of main study results***

Substance (INN/Invented Name): filgotinib					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.36			Potential PBT (N)
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined Fpen	1.28 (default) 2.12 (refined)	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Soil 1. K_{oc} 24384 2. K_{oc} 266815 3. K_{oc} 83378 Sludge 4.K_{oc} 149 5.K_{oc} 117			1.clay loam 2.sandy loam 3.loamy sand 4. loam 5. sand No trigger of terrestrial studies since <10000L/kg
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ =3-6 days $DT_{50, sediment}$ =110-127 days $DT_{50, whole\ system}$ =74 days % shifting to sediment = 76-91 at D14			Sediment study triggered
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	5.1	mg/L	*Raphidocelis subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.83	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	2.6	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEL	1000	mg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	456	mg/kg_{dwt}	*Chironomus riparius*

2.3.5. Discussion on non-clinical aspects

The preclinical studies are submitted in accordance with legal requirements and available guidelines. Scientific advice on non-clinical developmental program has been received and the CHMP advice have been adequately followed.

Pharmacology

A series of *in vitro* and *in vivo* studies (biochemical assays, cell experiments, whole blood assays and collagen induced arthritis (CIA)) have been conducted in order to characterize the primary pharmacology of filgotinib and the major metabolite GS-829845. *In vitro* it was demonstrated that filgotinib is a JAK family inhibitor. Filgotinib treatment of CIA in rats resulted in variable improvements of RA-similar clinical symptoms. The GS-829845 also exerts JAK inhibitory effects (with ~10 fold less potency) and when co-administered with filgotinib in the same exposure ratio as seen in humans enhanced PD effects were seen in the CIA rat model. In addition, primary pharmacodynamic studies have been done to compare

filgotinib with other JAK inhibitors. The SmPC 5.1 text, initially suggested by the Applicant, claiming that filgotinib is a "selective JAK1 inhibitor", was not agreed on. Filgotinib has not been convincingly demonstrated to be a specific JAK1 inhibitor as filgotinib (and/or GS-829845) may inhibit several of the JAK family members within the clinical Cmax; this is adequately reflected in the Section 5.1 of the SmPC.

Extensive off-target screening studies of over 450 kinases, 40 receptors and 22 enzymes have been performed with filgotinib and the main metabolite GS-829845. Filgotinib and GS-829845 appears to bind to some non JAK-kinase proteins at concentration below and near the clinical Cmax of ~6 μM and 9.8 μM, respectively. The clinical consequences of these putative bindings are unknown and was not discussed by the Applicant in the initial MAA. However, in the context of a question on the toxicity findings on the male reproductive system, clinical consequences were partly discussed. Some potential off-target molecules were scrutinized by the Applicant but without identifying any plausible mechanism for these toxicities.

In vitro binding screening and kinase activity profiling were performed in several studies including over 450 protein kinases, 70 receptors and 22 enzymes. Some kinases displayed IC50 values below the Cmax for filgotinib. For some kinase targets, competitive inhibition >50 % of ATP binding was observed, e.g. 95 % inhibition of LKB1 and 73 % inhibition of SRPK1. The Applicant argued that due to higher activity towards JAK1 than to these non-JAK kinases, no meaningful impact from these targets are expected. The CHMP did not agree with this argument. Even though filgotinib show 5 to 44-fold lower activity towards other kinases than to JAK1 itself, it is possible that filgotinib may interact with these non-JAK kinases at clinically relevant exposures. It is possible that such interaction may lead to non-traditionally JAK associated toxicity and adverse findings, e.g. testis toxicity (for example, in the *in vitro* screening study 159 some of the kinases (LKB1 and SRPK1) identified are highly abundant in testis and have been associated with spermatogenesis). The Applicant was invited to provide a discussion on what potential secondary pharmacodynamic effects off-target binding may results in, focusing on potentially interaction related to testis toxicity. Thus, the applicant discussed literature findings for LKB1 and SRPK1 but without being able to identify any mechanism that could explain the testis toxicity. In addition, the Applicant did not find any relevant data in the literature regarding potential effects of inhibiting FLT4, STK16, or YSK4 (MAP3K19).

Furthermore, a reanalysis of the original microarray dataset was performed in order to determine whether newer databases or methodologies could provide additional functional insights. Upon CHMP's request, the applicant submitted this reanalysis, along with a discussion on the study results but without being able to provide new insights on the mechanism of testicular toxicity (please, see also the non-clinical toxicology section 2.3.3.).

Overall, the applicant has not been able to identify a viable mechanism for the decreased fertility, impaired spermatogenesis and histopathological effects on male reproductive organs. It appears the search has been mostly focused on identifying a single mechanism/target as a cause of the observed toxicities. It could have been considered whether the findings on the male reproductive system are due to a combination of factors/mechanisms. However, the main focus for the CHMP is to understand whether the findings are clinically relevant. To this end, the data from the ongoing clinical MANTA study evaluating the impact on male fertility is expected to provide the most relevant information. The Applicant should submit the results of this study (see RMP- Section 2.7.).

No safety concerns have been identified in the safety pharmacology studies conducted with filgotinib and its main metabolite GS-829845. Some minor CV effects on HR and BP were noted but is considered to not be of clinical relevance.

In summary, from the *in vitro* studies it can be concluded that filgotinib, in the experimental setting, preferentially inhibits JAK1/JAK2 whereas JAK3 and TYK2 are inhibited to less degree but still at concentrations that may be of clinical relevance. The main metabolite GS-829845 displays 10-fold lower potency for all the JAKs as compared to filgotinib. The human cellular studies demonstrated that filgotinib

(and GS-829845 metabolite) inhibit signalling mediated by the cytokines IL6, IL2 and IFNα at clinically relevant concentrations. In rat CIA RA models, filgotinib treatment resulted in reduction of RA similar parameters. The PD effects were improved when co-administered with the GS-829845 metabolite. The overall PD effect in the animal model was mostly driven (>90%) by the metabolite GS-829845, which is reflected in SmPC in section 5.1.

Pharmacokinetics

The bioanalytical LC/MS/MS method used for quantification of filgotinib and its metabolite GS-829845 in the pivotal toxicity studies of rats, mice, rabbits and dogs have been performed according to GLP standard.

Absorption

In vivo the absorption of Filgotinib was studied in mice, rats, rabbits, dogs, monkeys and minipigs after oral and i.v. single dose administration. After oral administration Filgotinib is rapidly absorbed in all species studied with Tmax occurring after 1-2 hours. In all species the clearance is moderate/high (1.87-2.87 L/h/kg) and volume of distribution greater than total body water volume.

The bioavailability of filgotinib after oral intake ranges between 25 % and 82 % (being lowest in monkeys and highest in mouse) are indicative of various grades of first pass metabolism. The half-time (T ½) of 10 hours (mice), 8 h (monkeys) and 4.5-6 h (dog), 4 h (rat and rabbit) after PO intake is similar as the half-time seen in humans (5 h).

Rats, rabbits and dogs were also administered with GS-829845 to further study the PK parameters of this major metabolite. Single dose oral administration of the GS-829845 showed rapid absorption with Tmax 1-2 hours and half-life of 7 hours (rats), 6 hours (rabbit) and 9 hours (dogs), i.e. somewhat longer half-life than the parent compound filgotinib.

No PK data after repeat dosing were presented in the PKs overview but instead the Applicant referred to TK data from rat and dog toxicity studies. TK data after repeat dose of filgotinib did not indicate any evidence of accumulation of filgotinib and the GS-829845 metabolite, and no gender differences were discerned (see toxicology section 2.3.3.).

Distribution

The *in vitro* plasma protein binding of filgotinib and GS-829845 have been studied in mouse, rat, rabbit, dog, monkey and human. In all species, filgotinib and the metabolite show similar protein binding profile. The unbound fraction varies from 35-75 % with similar intra and inter-species differences. It was concluded that HSA (albumin) and AAG (alpha-1 acid glycoprotein) are the main plasma proteins involved (study GLPG0634-PK-002). When studied in presence of human hepatic microsomes, the unbound fraction of filgotinib and GS-829845 were only 14 and 5 %, respectively. Both filgotinib and GS metabolite showed whole blood/plasma concentrations around 1 in all species including humans.

The tissue distribution of total radioactivity in pigmented and non-pigmented rats were monitored following single oral dose administration and quantified by whole-body autoradiography. The distribution was studied with two different labelled variants; 14C-carboxy-Filgotinib and 14C-GS-Filgotinib. The later when hydrolysed, the GS-829845 metabolite is formed and consequently the total radioactivity will be a result of both filgotinib and the metabolite. Both the labelled filgotinib variants were rapidly absorbed and widely distributed through a variety of tissues reaching peak concentrations within 1 hour post administration in most tissues. According to the applicant, similar distribution with filgotinib and its metabolite GS-829845 is shown justified by the physiochemical properties, plasma and blood binding, PK

and distribution data, which is agreed. However, total distribution of GS-829845 was detailed neither in animal nor in human. This issue was no longer pursue by the CHMP.

High concentrations were found in the gastrointestinal (GI) and urinary bladder, consistent with elimination pathways with urine and faeces. Another notably finding was that highest concentrations were detected in uveal tract of the eye which declined after 5 hours. The concentrations of radioactivity were about 2-3 fold higher in pigmented skin than non-pigmented. The Applicant stated the lipophilic weak bases are known to be associated with melanin containing tissues and should not lead to any clinical consequences. The CHMP agreed, as filgotinib was evaluated in phototoxicity studies with the conclusion that filgotinib is not phototoxic (see toxicology section 2.3.3.).

In the testis, radioactivity was below the limit of quantification by 48 hours in bothrat studies, and concentrations at the other time points were similar or lower than observed in many other tissues. However, for the 14C-carboxy-filgotinib, a high concentration was observed in epididymides that remained the same after 24 h and after 48 hours post administration, i.e. in accordance with retention that have occurred. Since no time points after 48 h were included, it is not possible to evaluate the half-life time of filgotinib in epididymis. Nor is it possible to see if repeat-dosing may result in accumulation. No discussion of this notably finding was given by the Applicant. When 14C-filgotinib was used in the distribution studies, the same retention of radioactivity in epididymides was not found. The applicant explain that it is the different label positions of 14C-filgotinib and 14C-carboxy that accounts for the different distribution profiles in rats in that the [14C] carboxy filgotinib represent filgotinib , cyclopropane carboxylic acid (CPCA) and its metabolites while [14C] filgotinib represent filgotinib, GS 829845 and its metabolites. Indeed, greater [14C] carboxy levels compared to [14C] filgotinib levels would indicate the presence of CPCA and/or CPCA conjugates as observed in epididymis. This justification was acceptable to the CHMP.

Only 0.5 % of the total radioactivity was detected in the brain regardless of labelling variant used, so passing through the blood brain barrier appears low. The Applicant did not conduct any distribution studies to study if filgotinib was passing through placenta or excreted in milk. From repro and juvenile toxicity studies it can be concluded that filgotinib can be quantified in new-born pups of exposed mothers, as well in the milk of lactating mothers. This information is reflected in pre-clinical section 5.3 of the SmPC.

Metabolism

In vitro metabolism studies were conducted in hepatocytes from mouse, rat, dog, monkey and human. Three metabolites were identified, of which MF-2 (later known as GS-829845) was the only metabolite identified over 10 % of total radioactivity. Hence the other two metabolites MF-1 and MF-3 are of less relevance for toxicity studies.

In vivo filgotinib metabolism were studied in transgenic mouse, rat, dog and human but not in rabbit. Since embryo-foetal developmental studies were performed in rabbit, the Applicant, upon request, presented the metabolism pathway also in this species. All detected metabolites were comparable to those in the other animal species and in human.

In the transgenic mouse and in human, GS-8298845 was identified as the major circulating metabolite with radioactivity corresponding to 57 and 92 %. After single dose administration of filgotinib the concentrations of the main metabolite GS-829845 were analysed in mouse, rat, dog, monkey, minipig, and rabbit, and an exposures ratio between AUC for GS829845 and filgotinib were calculated. The AUC metabolite-to-parent ratio for AUC at steady state were below 1 in rat, dog, monkey, minipig and rabbit whereas in the mouse, GS-829845 was found at higher concentrations than filgotinib itself (AUC ratio of 1.57). This clearly demonstrates that neither of the non-clinical species are subject to an exposure ratio

of clinical relevance (the metabolite to parent ratio for AUC ratio in humans is 16-21). Therefore, the Applicant has carried out specific toxicity studies (REPRO toxicity, repeat dose toxicity, genotoxicity and cancer studies) with GS-S829845 in order to evaluate the toxicity of GS-829845 itself and when co-administered with filgotinib in ratios mimicking the exposure ratio in humans.

The conjugated metabolite CPCA carnitine was not detected as a radioactive metabolite due to the labelling position but was estimated to be around 20 % of total drug exposure in humans. As this metabolite is formed in dog and mouse with similar exposure rates (Cmax and AUC) this metabolite is considered to have been sufficiently assessed in dog and mouse throughout the toxicity studies.

So, in summary, from a PK point of view the species (i.e. rats, dogs, rabbits and mice) used in the toxicity studies of filgotinib have been adequately justified by the Applicant.

Toxicology

Relevance of animal models

The applicant has provided data on JAK inhibitory effects in mice and rats indicating that there is a cross-reactivity in these species which could qualify them as relevant toxicological species. However, no such data has been presented for dogs and rabbits. The applicant´s justification for this is based on the high sequence homology of the JAK family between species, data from other JAK-inhibitors that indicate similar inhibitory response between species and that dogs and rabbits has been considered as relevant species with these other JAK-inhibitors. It is *de facto* that cross-reactivity of filgotinib has not been tested in these species which is expected before inclusion in toxicology studies. However, this issue was no longer pursue by the CHMP.

Reproductive toxicity

Filgotinib related adverse effects were observed in male reproductive system including microscopic testicular changes and reduced spermatogenesis and fertility. The lesions in testis consisted of germ cell depletion/degeneration and/or tubular vacuolation with correlating changes in epididymides (reduced sperm content and/or increased cell debris) and was observed in mice, rats and dogs with dogs being most sensitive. In dogs, effects were observed already after 4-weeks of administration while in rats, effects were seen after 13 weeks. In dogs, adverse testicular effects were observed at AUC exposure margins from 0.9-fold of the clinical exposure at 200mg. In fertility studies in rats, reduced male fertility (5% fertility) and marked testicular lesions and marked reduced sperm quality and quantity occurred at 60 mg/kg/day with a NOAEL at 30 mg/kg/day which corresponds to approximately a 3-fold AUC exposure marginal to the clinical daily dose at 200 mg.

Filgotinib related adverse effects on female fertility was observed at the same dose and included increased post implantation loss due to increased early and late resorptions. At LOAEL for male reproductive organs generally no changes of hormonal levels or seminology parameters were observed apart from increased LH levels in rats. At higher doses (and exposure) a decrease of testosterone, FSH and inhibin levels was observed in rats while in dogs no changes of testosterone or FSH levels occurred at any dose. Partial reversibility was observed in dogs treated for 13 weeks and 8 weeks of recovery with reduced number of sperms and normal sperms without microscopic testicular changes. In a mechanistic study in rats, filgotinib did not affect the transcription of genes relevant to the JAK pathway in testis and the gene expression observed did not match any profile published or within public database. However, other possibilities that is not related to the JAK pathway may exist for example cross reactivity to kinases and receptors potentially expressed in testis.

Another potential mechanism contributing to impaired spermatogenesis may be related to carnitine, e.g. it is possible that the CPCA-carnitine formation may result in a depletion of carnitine. Carnitine, known to exert anti-oxidative effects is highly concentrated in epididymis and play a crucial role in sperm metabolism and maturation. Positive correlations between seminal concentrations and sperm count/motility have been found in clinical studies, and carnitine can function as marker of epididymal function. However, carnitine appears not to have been monitored in the preclinical studies and no discussion on carnitine impact on male infertility have been provided in the non-clinical dossier. The applicant proposed that a secondary effect caused by alteration of carnitine levels may be of minor relevance, referring to the low concentration of CPCA in plasma and urine and that no effects on testes was observed in a FDA 90-day rat study evaluating CPCA toxicity, but instead may be a direct effect by filgotinib which seems reasonable. Furthermore, with the clinical daily dose of 200mg/kg filgotinib the daily dietary intake or biosynthesis of carnitine overcome the potential loss further support a minimal risk of alteration of carnitine homeostasis causing a potential effect on male reproductive organs.

Effects on male reproductive system were observed in dogs also with the metabolite GS-829845 after 13-week treatment at doses ≥ 20 mg/kg/day. However, after longer duration of treatment, no testicular findings were observed up to 30 mg/kg/day after 26-week exposure and testicular findings observed at 15 and 30 mg/kg/d after 39-week exposure were not considered adverse as they corresponded to those observed in the control groups.

In summary, the mechanism behind the testicular toxicity remains unknown. At the CHMP's request, the applicant proposed a stringent warning in section 4.4 of the SmPC to mitigate the risk regarding male fertility which was considered acceptable to the CHMP. In addition, adequate risk minimisation measures have been proposed by the Applicant. This risk is addressed in the educational material with the aim to limit the use of filgotinib to female patients and male patients without intent of fathering a child.

The applicant considers the increased Leydig cell tumours to be related to a rat-specific mechanism involving increasing levels of LH that is linked to increase in rat Leydig cells tumours referring to Cook et al. 1999 and Chapin 2016 who further states that rat Leydig cells are considerably more sensitive to LH than human Leydig cells due to an increased number of LH receptors and an increased sensitivity. In the rat repeated toxicity studies filgotinib induced increased levels of LH (at 45 mg/kg daily dose for 39-weeks the LH levels increased with a 2-fold and dosing of 180 mg/kg increases were 6-fold compared to control animals) and Leydig cell hyperplasia at 60 mg/kg. Considering this it is likely to think that increases of LH occurred also in rats after two years of dosing with filgotinib. Based on that LH is a known inducer of Leydig cell tumours in rodents and the known major differences between rodent and humans with respect to prevalence of different testicular tumour types, hormonal physiology and response and risk factors for Leydig cell tumours the CHMP agreed that the observed Leydig cell tumours are of little relevance for humans.

Combinate toxicity of filgotinib and GS-829845

One pilot 14-day study in rat raised concern about safety of the combination filgotinib/GS-829845, when administrated at ratio 1/6. NOAEL was determined based on male reproductive effect and this NOAEL determined in rat for the combination (10/60 mg/kg/day) was lower than the NOAEL determined when filgotinib and GS-829845 were administrated separately (filgotinib 4-w study: NOAEL > 45 mg/kg/d, 13-w and 26w-studies: 20 mg/kg/day and GS-829845 no effect on male reproductive system up to 26 weeks, NOAEL > 180 mg/kg/day). Indeed, the observed testicular findings after combination administration were at similar exposure than after administration of filgotinib alone. Co administration of filgotinib with its metabolite did not result in exacerbation of testicular toxicity.

Immunosuppression

Effects consistent with the inhibition of JAK1/3 (reduced circulating lymphocytes and NK-cells with correlating changes in lymphoid tissues) were observed in nearly all dose levels in repeated dose toxicity studies of all species assessed after administration of either filgotinib or GS-829845. Adverse, but reversible, effects were observed in rats from 20 mg/kg/day (1.6x clinical exposure) and in dogs from 15 mg/kg/day (6x clinical exposure) after administration with filgotinib. Furthermore, effects consistent with JAK-2 inhibition (RBC parameters and reticulocytes) were observed in mice, rats and dogs administrated with filgotinib but without obvious effects with GS-829845. In rats, reduced RBC parameters were observed at doses from 100 mg/kg/day and in dogs at 5 mg/kg/day. The NOAEL for JAK-1 and JAK-2 related changes were with filgotinib 45 mg/kg/day in rat and 5 and 2.5 mg/kg/day in dogs corresponding to 5.9-fold and 1.8- and 1.1-fold, respectively, compared to the AUC clinical exposure at 200mg/kg.

Carcinogenic potential

Filgotinib can be considered as not genotoxic or clastogenic.

Filgotinib (but not GS-829845) induced increased incidence of testis Leydig cell tumours in male rats. This is likely a rodent specific finding with little relevance for humans based on that filgotinib (but not GS-829845) induce increased levels of LH in rats which is a known inducer of Leydig cell tumours in rodents and the known major differences between rodent and humans with respect to prevalence of different testicular tumour types, hormonal physiology and response and risk factors for Leydig cell tumours. The Applicant concluded that the increase in Leydig cell hyperplasia/adenomas at exposures approximately 2.6 times the 200 mg filgotinib dose in the 2-year carcinogenicity study is not considered clinically relevant, which seems reasonable to the CHMP. Section 5.3 of the SmPC was updated accordingly.

Developmental toxicity

Filgotinib and GS-829845 produced embryotoxicity and teratogenicity in rats and rabbits. Increased post implantation loss and a decrease number of live foetuses and foetal body weight were observed at high filgotinib dose (100mg/kg). Visceral and/or skeletal abnormalities occurred at all doses with filgotinib and GS-829845. Dose-related increase in incidence of abnormalities included, among others, vertebrate and sternal abnormalities, rudimentary ribs, dilated/convoluted ureter, internal hydrocephaly, and absent or small eyes. No NOAEL was established. The AUC exposure at the lowest dose corresponded to 2.4-fold (filgotinib) and 1.7-fold (GS-829845) to the clinical exposure at 200 mg. Similar effects were observed in rabbits including increased post implantation loss and a decreased number of live fetuses and fetal body weight at high doses and visceral and/or skeletal abnormalities at all dose levels. No NOAEL was established. The AUC exposure at the lowest dose corresponded to 1.4-fold (filgotinib) and 4.9-fold (GS-829845) to the clinical exposure at 200 mg. The applicant has addressed the embryotoxic and teratogenic effects of filgotinib and included pregnancy as contraindication in the SmPC.

In a pre- and postnatal development study in rats no adverse effects occurred at any dose. The AUC exposure at the highest dose of filgotinib (15 mg/kg/day) and GS-829845 (30 mg/kg/day) corresponded to a 1.2-fold and 0.8-fold marginal, respectively, to the clinical dose at 200 mg/kg/day. It can be concluded that this study is not conclusive due to the low exposure of the animals. In the section 5.3 of the SmPC it is reflected that F1 offspring have not been sufficiently exposed and that the pre- and postnatal development rat study is therefore not conclusive.

In conclusion, filgotinib and GS-829845 is teratogenic in rats and rabbits inducing visceral and skeletal malformations with no exposure marginals to the clinical dose at 200 mg/day. The applicant has addressed this issue and included pregnancy as contraindication in the SmPC.

Effects on teeth

Filgotinib related effects on incisor teeth was observed in rats only, including changes in the lower incisor tooth enamel, termed striae, at 45 mg/kg/day and slight to marked degeneration/loss/disorganization of ameloblast accompanied with malformed enamel at 100 mg/kg/day. The NOAEL for these findings was set to 20 mg/kg/day corresponding to 2.8-fold of the clinical AUC exposure at 200 mg/kg. No corresponding findings were observed in juvenile rats (up to postnatal day 183) dosed up to 20 mg/kg/day. The applicant argued that these findings are not relevant for humans as rat incisors grow throughout their lives and are therefore continuously depositing new enamel while in humans enamel formation is complete once secondary dentition is finished, generally, in the late teens. However, a potential risk for humans, in terms of adolescent and paediatric patients, cannot be ruled out. The applicant has agreed a PIP with EMA (EMEA 001619 PIP04 17 M01) for RA indication in paediatric patients and dosing regimen and PK blood sampling will be agreed with PDCO before initiation of treatment to minimize potential risks observed in non-clinical studies including effects on incisor teeth, which is acknowledged. At the CHMP's request, the effects on incisor teeth in rats are addressed in the SmPC section 5.3.

Impurities

The Applicant's strategy to perform directly *in vivo* genotoxicity studies on impurities GS 831208 and GS 830681 is acceptable. Indeed, this strategy based on the provided literature references for *in vitro* results and the PigA and Comet assays selection are justified. Therefore, impurities GS 831208 and GS 830681 could be considered as ICH M7 Class 5 impurity (non-mutagenic impurity) and controlled as such.

Environmental risk assessment

Filgotinib was found to be very persistent in the sediment compartment but is not considered as a PBT or vPvB substance. One transformation product U1 is identical with the major metabolite GS-845829 and this should be stated within an updated ERA. Based on a complete Phase II assessment it can be concluded that no environmental effects are expected following the use of filgotinib.

2.3.6. Conclusion on the non-clinical aspects

From the *in vitro* PD studies, it can be concluded that filgotinib is a JAK family inhibitor with some preference for JAK1 or JAK1/JAK3. In absence of a JAK3 selective cellular assay, the relative contribution of JAK3 vs JAK1 inhibitory activity at the cellular level cannot be concluded. There were equivocal findings on selective inhibition of JAK1 over JAK2 with whole blood assay showing a >14-fold JAK1 selectivity but other cellular assays and biochemical binding showing less convincing results. Overall, the clinical Cmax for filgotinib is well above the observed Kd values for all JAK family members, consequently inhibition of any of these cannot entirely be ruled out. The main metabolite GS-829845 display 10-fold lower potency and contribute to PD effects when administered to CIA rats in similar exposure AUC ratio as observed in humans. All metabolites have been adequately exposed in the toxicity studies.

The toxicological program revealed that filgotinib induced adverse effects on male reproductive system and fertility. Despite further investigations, intended to shed light on potential mechanisms for the toxicity, no further understanding has been gained. Thus, the clinical relevance of these findings is unknown. However, it seems clear that the toxicity is caused by filgotinib, and not by GS 829845, the major metabolite of filgotinib. At the CHMP's request, the applicant proposed a stringent warning in

section 4.4 of the SmPC to mitigate the risk regarding male fertility which was considered acceptable to the CHMP. In addition, adequate risk minimisation measures have been proposed by the Applicant. This risk is addressed in the educational material with the aim to limit the use of filgotinib to female patients and male patients without intent of fathering a child. Finally, the data from the ongoing clinical MANTA study evaluating the impact on male fertility is expected to provide an understanding as to whether the findings are clinically relevant (see RMP – Section 2.7.).

Furthermore, the toxicology program revealed that filgotinib and the human metabolite GS-829845 have embryotoxic and teratogenic potential at low exposures compared to that of the intended clinical dose. Therefore, filgotinib is contraindicated during pregnancy.

There were no concerns of human relevance regarding carcinogenic potential. Filgotinib or GS-829845 is not considered mutagenic, clastogenic or phototoxic.

In summary, the application is acceptable from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The 4 phase II (+extension) and the 3 phase III studies (+extension) that contributed to the characterization of the clinical pharmacology of filgotinib are presented in the clinical efficacy section 2.5. of this assessment report. An overview of the phase I clinical pharmacology studies is presented in Table 4.

Table 4 Overview of Phase 1 Clinical Studies Contributing to the Characterization of the Clinical Pharmacology of Filgotinib

Study Number	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number)	n[a]	
Phase 1 Studies				
GLPG0634-CL-101	Phase 1, first-in-human, single and multiple ascending dose study in healthy subjects	1, 3, or 10 mg filgotinib powder (10G05) filgotinib 10-mg capsule (10G09) filgotinib 25-mg capsule (10G19) filgotinib 50-mg capsule (10G13, 11B02) filgotinib 100-mg capsule (10G14, 11B03) 2 × filgotinib 100-mg capsules (10G14, 11B03)	48	Placebo
GLPG0634-CL-102	Phase 1 multiple ascending dose study in healthy subjects	3 × filgotinib 100-mg capsules (11G18) 4 × filgotinib 100-mg capsules (11G18) + filgotinib 50-mg capsule (11G15)	12	Placebo
GLPG0634-CL-103	Phase 1 study to access the effect of filgotinib on the PK of midazolam in healthy male subjects	2 × filgotinib 100-mg capsules (1280-0266) + 2 mg MDZ oral syrup	20	2 mg MDZ oral syrup
GLPG0634-CL-104	Phase 1 study to characterize the PK of filgotinib and its metabolites in elderly healthy subjects	filgotinib 100-mg capsule (1280 0145)	30	None
GLPG0634-CL-105	Phase 1 mass balance study to investigate the PK and metabolism of filgotinib in healthy male subjects	100 mg [14C]filgotinib, containing not more than 6.13 MBq (1.0 mSv) of 14C, dissolved in a reconstitution solvent (114504/C/02-1 to 114504/C/02-6)	6	None
GLPG0634-CL-106	Phase 1 study in subjects with impaired renal function	filgotinib 100-mg tablet (14800005)	24	None
GLPG0634-CL-110	Phase 1 study in Japanese and Caucasian healthy subjects designed to evaluate PK/PD, safety, and tolerability of multiple study drug doses	2 × filgotinib 25-mg tablets (4102) filgotinib 100-mg tablet (4209) 2 × filgotinib 100-mg tablets (4209)	24	Placebo

Study Number	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number)	n[a]	
GS-US-417-3900	Phase 1 study to compare the rBA of 2 tablet formulations of filgotinib, evaluate food effect, and evaluate the effect of ARAs or P-gp inhibitors on the PK of filgotinib	1 × filgotinib 100-mg new tablet (EV1601D1) 1 × filgotinib 200-mg new tablet (EV1601F1) 1 × filgotinib 200-mg new tablet (EV1601F1) + omeprazole (40 mg) 1 × filgotinib 200-mg new tablet (EV1601F1) + famotidine (40 mg) 1 × filgotinib 100-mg new tablet (EV1601D1) + itraconazole (200 mg)	104	1 × filgotinib 100-mg reference tablet 2 × filgotinib 100-mg reference tablets 1 × filgotinib 200-mg new tablet 1 × filgotinib 100-mg new tablet
GS-US-417-3911	Phase 1 study to evaluate the effect of filgotinib on the QT/QTc interval in healthy subjects	1 × filgotinib 200-mg tablet (EV1601F1) 3 × filgotinib 150-mg tablet (EV1601E1)	52	Moxifloxacin (400 mg) Placebo
GS-US-417-3916	Phase 1 study to evaluate the effect of filgotinib on the PK of an OC medication	1 × filgotinib 200-mg tablet (EV1601F1) + 30 mcg ethinyl estradiol/150 mcg levonorgestrel	24	30 mcg ethinyl estradiol/150 mcg levonorgestrel
GS-US-417-4107	Phase 1 study to evaluate potential transporter-mediated DDIs with filgotinib	1 × filgotinib 200-mg tablet (EV1715B1) + rifampin (600 mg) 1 × filgotinib 200-mg tablet (EV1715B1) + metformin (850 mg)	26	1 × filgotinib 200-mg tablet
GS-US-417-4048	Phase 1 study in subjects with impaired hepatic function	1 × filgotinib 100-mg tablet (EV1708B1)	20	None

ARA = acid-reducing agent; DDI = drug-drug interaction; MDZ = midazolam; OC = oral contraceptive; PD = pharmacodynamics; P-gp = P-glycoprotein; PK = pharmacokinetic(s); QTc = QT interval corrected for heart rate; rBA = relative bioavailability

a Number of subjects who were administered any the test treatment (ie, number does not include subjects who received reference treatment).

2.4.2. Pharmacokinetics

The systemic plasma concentration of the major metabolite GS-829845 was ca 15-fold compared to the exposure of filgotinib following oral administration of recommended doses. The *in vitro* activity of GS-829845 is about 1/10 of the activity of filgotinib.

The objectives of the population PK analysis were to determine the effects of intrinsic and extrinsic factors on the PK of filgotinib and GS-829845 to better understand clinical factors that might affect exposure in individual subjects, and to provide model predicted individual subject PK parameter estimates from PopPK models for exposure-response analysis. Separate models were developed for filgotinib and its metabolite GS-829845.

As both filgotinib and its metabolite GS-829845 contribute to efficacy, their exposures (active moiety) were combined into a single parameter, AUCeff. The exposure-safety analyses were performed separately for filgotinib and GS-829845 to characterize the individual safety profiles of each analyte.

Bioanalysis

Plasma concentrations of filgotinib and GS-829845 (major metabolite) have been determined simultaneously by using LC-MS/MS methods following validations/partially validations. The method was further developed during the development and transferred to different contract research organisations (CROs). In the final method, filgotinib-d4 and GS-829845-d4 were used as internal standards. The calibration range was set to 1-2000 ng/ml for filgotinib and 2-4000 ng/ml for GS-829845. Within study validations have been performed.

Filgotinib and GS-829845 concentrations in the urine were determined simultaneously by LC-MS/MS using either filgotinib-d4 or filgotinib-d5 as internal standard. The calibration range was 1-1000 ng/ml for both filgotinib and GS-829845. The assay was transferred to different CROs and appropriately validated.

An LC-MS/MS method was used and qualified for determination of CPCA (cyclopropane carboxylic acid) and conjugates in plasma and urine. CPCA-d5 was used as internal standard and the calibration range was 5-5000 ng/ml and 10-5000 ng/ml for CPCA in plasma and urine, respectively. Assays for determination of CPCA-conjugates (CPCA-carnitine, glycine and taurine) were qualified using CPCA-carnitine-d5, CPCA-glycine-d5, and CPCA-taurine-d5 were used as internal standards.

Following co-administration of midazolam, oral contraceptive, metformin and methotrexate, plasma concentrations of midazolam, 1-OH-midazolam and 4-OH-midazolam, norgestrel, norgestimate, ethinyl estradiol, metformin, methotrexate and 7-OH-methotrexate appropriately determined using available methods at CROs.

Absorption

Filgotinib is characterized as a BCS-II compound *i.e.* high permeability, low solubility. Both filgotinib and GS-829845 are characterized as Pgp substrate *in vitro.*

Filgotinib was rapidly absorbed, with a t_{max} dependent on formulation 0.5-1h and 1-3h following administration a solution and a capsule, respectively. T_{max} was determined to 1-3 h following administration of filgotinib 200 mg.

Steady state was reached on Day 2 and Day 4 for filgotinib and GS-829845 following repeated dosing. The R_{AC} (accumulation ratio) was 1.1 for filgotinib and 2.2 for GS-829845 after filgotinib 200 mg od.

A fairly dose-proportionality in the PK was seen at doses <100 mg but a more than dose-proportional increase at doses of ≥100 mg (*Figure 2*).

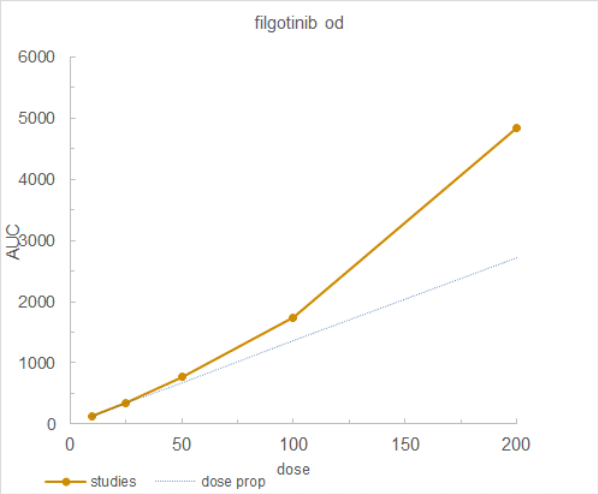


Figure 2: AUC versus oral doses of filgotinib

More than 85% of the dose was absorbed, as 87% of a 14C-filgotinib-dose was excreted in the urine .

No clinically relevant difference in systemic exposure was seen following filgotinib 200 mg without and with food (high fat meal). C_{max} and AUC_{inf} of filgotinib was 0.8-fold and 1-fold, respectively, and for GS-829845 0.9-fold and 1.0-fold when given together with food compared to without.

Formulation development continued during the whole development program of filgotinib. Different formulations have been used in the clinical pharmacology program - oral solution, capsule and "early" tablet except in the drug-drug interaction (DDI) study with transporter proteins where the "new" tablet was used. The "new" tablet was further developed during phase 3, where only the composition of the tablet was modified qualitatively but not quantitatively.

- The capsule (filgotinib-HCl) was not bioequivalent (BE) to the "early" tablet (filgotinib-HCl) after filgotinib 200 mg – fasted state tablet/capsule ratio of C_{max} 1.04 (90%CI 0.80-1.35) and AUC_{inf} 1.16 (90%CI 0.99-1.36). No difference in GS-829845 between the two formulations.
- The "new" (commercial; filgotinib-maleate) tablet 200 mg was BE to the early tablet 100 mgx2 – "new"/early tablet ratio of C_{max} 1.01 (90%CI 0.87-1.18) and AUC_{inf} 0.97 (90%CI 0.91-1.04). No difference in GS-829845 between the two formulations.

Distribution

The f_u (unbound fraction) of filgotinib 4 µg/ml and GS-829845 20 µg/ml were determined to 0.45 and 0.66, respectively.

Similar f_u of filgotinib was seen in plasma from patients with moderate hepatic impairment (HI) 0.44 compared to 0.41 in plasma from healthy subjects. For GS-829845 f_u was 0.61 in moderate HI and 0.55 in subjects with normal hepatic function.

The *in vitro* C_B/C_P ratio (at 0.5 µM) was determined to 1 and 1.4 for filgotinib and GS-829845, respectively.

Filgotinib and GS-829845 are substrates of the glycoprotein P (P-gp) transporter.

Elimination

The terminal $t_{1/2}$ (half-life) of filgotinib was calculated to approximately 7h and the $t_{1/2}$ for the major metabolite GS-829845 was 19-27h.

The excretion of 14C-filgotinib 100 mg (6.1 MBq) was studied in healthy subjects (n=6) following a single, oral dose in fed state. Eighty-seven percent (87%; range 80-94%) of the administered dose (14C-filgotinib) was excreted in the urine and 15% (range 11-22%) in faeces.

The excretion was rapid with approximately half of the radioactivity excreted within the first 24-h period after administration.

About 9% and 4% of the 14C-filgotinib dose was excreted as parent compound in the urine and faeces, respectively.

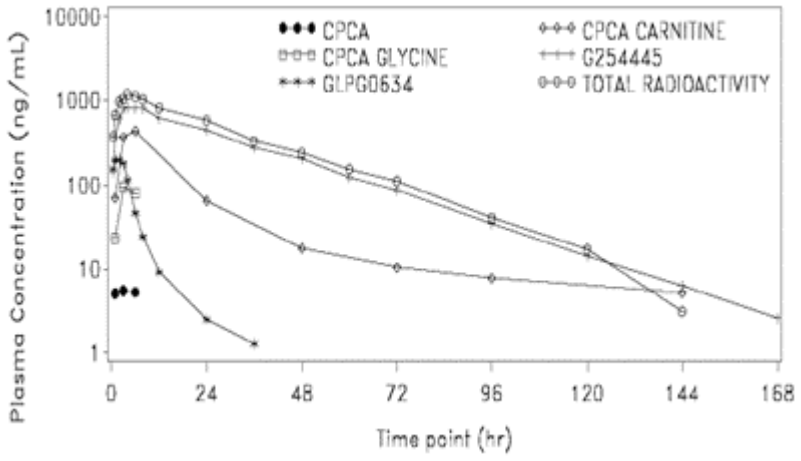
Metabolism

The main elimination pathway for filgotinib is *via* hydrolysis of the amide bond to GS-829845 and CPCA (cyclopropane carboxylic acid). *In vitro* metabolic identification suggested that filgotinib was mainly metabolized by CES2 (carboxylesterase 2) but also to a minor degree by CES1b and CES1c. Expression data from intestinal and liver S9 samples suggests that CES2 is expected to be the predominant enzyme overall, and that CES1 will play a larger role in hepatic metabolism of filgotinib versus intestinal metabolism.

One major metabolite was identified, following a single dose 14C-filgotinib 100 mg, with 54% and 9% of the dose excreted as GS-829845 in urine and faces, respectively. Even more was metabolized *via* that way as 15% and 2% of the dose were identified as GS-829845-N-glucuronide in the urine and faeces, respectively. Thus 80% of the dose is eliminated *via* the GS-829845 metabolic pathway.

Six further metabolites were observed in the urine and faeces and each of them was excreted as<2% of the dose in faeces and urine, respectively.

The systemic exposure of the main plasma metabolite GS-829845, CPCA-carnitine and CPCA-glycine was 15-, 7- and 0.4-fold of the exposure of filgotinib, respectively.



Filgotinib=GLPG0634; GS829845=G254445

Figure 3 *Plasma concentration vs time profiles of total radioactivity, filgotinib and detected plasma metabolites following a single oral dose of 14C-filgotinib 100 mg (6.1 MBq)*

The basic PK of GS-829845 has been determined after both single doses and at steady state. The $t_{1/2}$, 19-27h, was comparable with the $t_{1/2}$ of total plasma radioactivity. The R_{AC} was 1.8-2.2-fold at once daily dosing.

The $t_{1/2}$ of CPCA-carnitine was calculated to 49h following a single dose 14C-filgotinib 100 mg.

Dose proportionality and time dependencies

Time dependency

Both filgotinib and GS-829845 do not show signs of time-dependent PK, as seen from their respective PK parameters in the Table 5 and Table 6.

Table 5 Filgotinib Plasma Pharmacokinetic Parameters Following a Single Dose or Following Once Daily or Twice Daily Dosing of Filgotinib for 10 Days

Single Dose	**PK Parameter Mean (%CV)**	**50 mg (N = 5)**	**100 mg (N = 4)**	**200 mg (N = 4)**	**300 mg (N = 6)**
	AUC_{inf} (ng•h/mL)	771 (16.2)	1743 (14.3)	4844 (12.3)	4600 (18.2)[a]
Multiple Dose	**PK Parameter Mean (%CV)**	**50 mg BID (N = 6)**	**100 mg BID (N = 6)**	**200 mg QD (N = 6)**	**300 mg QD (N = 6)**
	AUC_{tau} (ng•h/mL)	758 (23.0)	2377 (42.3)	4447 (30.0)	4400 (17.2)

a AUC_{0-24}

Source: GLPG0634-CL-101, Supporting Data Display 11 and Supporting Data Display 32; GLPG0634-CL-102, Supporting Data Display 13

Table 6 GS-829845 Plasma Pharmacokinetic Parameters Following a Single Dose or Following Once Daily or Twice Daily Dosing of Filgotinib for 10 Days

Single Dose	**PK Parameter Mean (%CV)**	**50 mg (N = 6)**	**100 mg (N = 6)**	**200 mg (N = 6)**	**300 mg (N = 6)**
	AUC_{inf} (µg•h/mL)	15.6 (21.2)	30.2 (17.2)	63.8 (22.2)	NA
Multiple Dose	**PK Parameter Mean (%CV)**	**50 mg BID (N = 6)**	**100 mg BID (N = 6)**	**200 mg QD (N = 6)**	**300 mg QD (N = 6)**
	AUC_{tau} (µg•h/mL)	15.2 (10.2)	41.1 (12.9)	69.9 (25.6)	66.1 (15.8)

Source: GLPG0634-CL-101, Supporting Data Display 21 and Supporting Data Display 40; GLPG0634-CL-102, Supporting Data Display 22

Intra- and inter-individual variability

Since the population PK analysis was deemed inadequate, data from a DDI study with the commercial formulation (study GS-US-417-4107) and phase 3 data were used to describe variability, see Table 7.

Table 7 PK parameters and their variability with the commercial formulation and in phase 3 studies

		Phase 1 Studies		Pivotal Phase 3 Studies
Analyte	PK Parameter	GS-US-417-4107*		GS-US-417-0301 GS-US-417-0302 GS-US-417-0303
		Single dose	Multi dose	
		N=14	N=12	N=37
Filgotinib	AUC_{inf} or AUC_{tau} (hr.ng/mL)	6979.5 (24.6)	4672.2 (36.2)	6768.3 (43.7)
	C_{max} (ng/mL)	2194.3 (31.7)	1617.8 (41.7)	2154.6 (48.1)
	T_{max} (hr)	1.0 (1.0, 2.0)	1.5 (1.0, 2.3)	1.0 (0.5, 1.9)
GS-829845	AUC_{inf} or AUC_{tau} (hr.ng/mL)	77397.9 (25.3)	58932.9 (18.3)	83246.4 (27.3)
	C_{max} (ng/mL)	2897.9 (15.1)	3598.3 (13.2)	4427.8 (29.3)
	T_{max} (hr)	4.0 (3.0, 4.0)	3.5 (3.0, 4.0)	3.9 (2.0, 5.7)

*used the commercial formulation
AUC and C_{max} presented as mean (%CV); T_{max} presented as median (Q1, Q3); Phase 3 data from pooled intensive PK substudies

Population pharmacokinetic analysis

The population PK analysis of filgotinib and GS-829845 included data from 7 Phase 1 clinical studies in healthy subjects, 4 Phase 2 clinical studies in subjects with RA and 3 Phase 3 clinical studies in subjects with RA.

The final model of Filgotinib

The final filgotinib model was described by a 2-compartment model, with a mixture model for absorption and linear elimination.

The η-shrinkage for apparent oral clearance (CL/F), apparent central volume Vc/F, ka and D1 was 25%, 52%, 45% and 51%, respectively, and the ε-shrinkage was 12%. The final model parameter estimates are presented in Table 8.

Capsules and tablets were found to have different relative bioavailability(F) with capsules showing a 34% lower F. Weight effects were included on CL/F, apparent intercompartmental clearance (Q/F), Vc/F and apparent peripheral volume of distribution (Vp/F) using fixed allometric exponents of 0.75 for the clearance (CL) and 1 for the volume of distribution (V) parameters. Moreover, baseline C-reactive protein (bCRP) and sex female (SEXF) were identified as statistically significant covariates on filgotinib CL/F, whereas race (white and Asian versus black or African American versus other) were identified as a statistically significant covariate on Vc/F. Covariates were also examined to explain the mixture absorption model, but none of the available covariates could explain the difference in the absorption profiles observed.

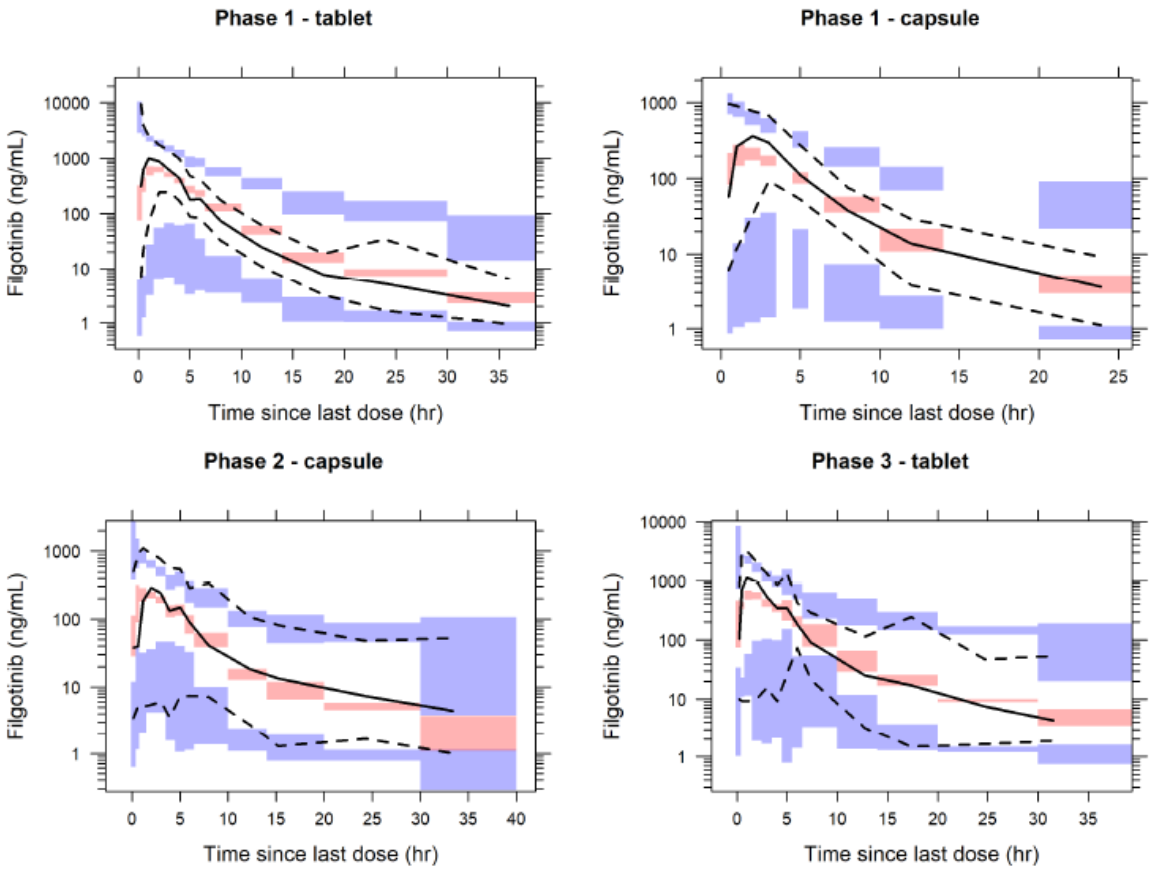
Table 8 Summary of the final model PK parameters estimates for Filgotinib and bootstrap and SIR results

Parameter	Parameter Description	Estimate [RSE[a]]	Bootstrap Estimate Median [2.5th and 97.5th Percentiles]	SIR Median [2.5th and 97.5th Percentiles]
$\exp(\theta_1)$	Apparent oral clearance (L/h)	35 [2]	36 [34.8;36.3]	35.5 [30.6;40.6]
$\exp(\theta_2)$	Apparent central volume (L)	104 [2.9]	106 [103;109]	105 [82;131]
$\exp(\theta_6)$	Apparent peripheral volume (L)	34.3 [4]	35.1 [32.9;35.9]	35.5 [27.5;48.4]
$\exp(\theta_5)$	Intercompartmental clearance (L/h)	3.37 [9.3]	3.35 [3.17;3.57]	3.37 [2.53;4.12]
$\frac{\exp(\theta_1)}{\exp(\theta_2)} + \exp$	Absorption rate constant (slower) (1/h)	2.07 [Fixed]	--	--
$\exp(\theta_4)$	Duration (h)	0.629 [Fixed]	--	--
θ_{11}	Capsule effect on F1	-0.338 [Fixed]	--	--
θ_{13}	CRP effect on CL/F (power)	-0.0295 [4.5]	-0.0324 [-0.0389;-0.0285]	-0.0297 [-0.0322;-0.0271]
θ_{14}	Male effect on CL/F	0.117 [17.9]	0.0737 [0.0678;0.113]	0.119 [0.0789;0.161]
θ_{15}	Weight effect on CL/F (power)	0.75 [Fixed]	--	--
θ_{19}	Weight effect on V_c/F (power)	1 [Fixed]	--	--
θ_{17}	Other race effect on V_c/F	0.309 [19.5]	0.351 [0.282;0.471]	0.31 [0.186;0.422]
θ_{18}	Black or African Am. race effect on V_c/F	-0.17 [35.3]	-0.14 [-0.19;-0.0766]	-0.177 [-0.285;-0.0489]
θ_{10}	Mixture slower absorption	0.818 [7.4]	0.823 [0.784;0.865]	0.807 [0.678;0.931]
θ_8	Proportional residual error (%)	66 [4.9]	65.2 [64.9;66]	65.7 [62.9;68.7]
$\omega^2 11$	Between subject variance on CL/F (%)	26 [4.8]	27 [26.2;27.8]	26.2 [24.8;27.5]
$\omega 21$	Correlation CL/F-V_c/F	0.0304 [16.3]	0.0509 [0.0402;0.0553]	0.0314 [0.0186;0.0382]
$\omega^2 22$	Between subject variance on V_c/F (%)	42 [9.8]	46.2 [41;47.1]	41.6 [37.3;45.1]
$\omega^2 33$	Between subject variance on k_a – slower (%)	166 [13.9]	177 [176;184]	169 [138;187]
$\omega^2 44$	Between subject variance on D1 (%)	200 [11.5]	199 [195;205]	201 [173;220]

Am. = American; CL/F = apparent oral clearance; CRP = C-reactive proteinD1 = duration; F1 = relative bioavailability; RSE = residual standard error; SD = standard deviation; SE = standard error; SIR = sampling importance resampling; V_c/F = apparent central volume.

a RSE is defined as the SE divided by the absolute value of the estimate ($|\theta|$) × 100% for nontransformed parameters and as SE × 100% for log-transformed parameters. RSEs are based on the SIR results.

Source: filgotinib-gof-all-final-run547-20200116.R



CI = confidence interval; DV = observed concentrations; pcVPC = prediction-corrected visual predictive check.
The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in a
subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and
95th percentiles. The pcVPC is stratified by phase and formulation.
Source: filgotinib_gof_all_final_run547_20200116.R

Figure 4 pcVPC of Filgotinib Plasma Concentration-Time Profile Stratified by Phase and Formulation

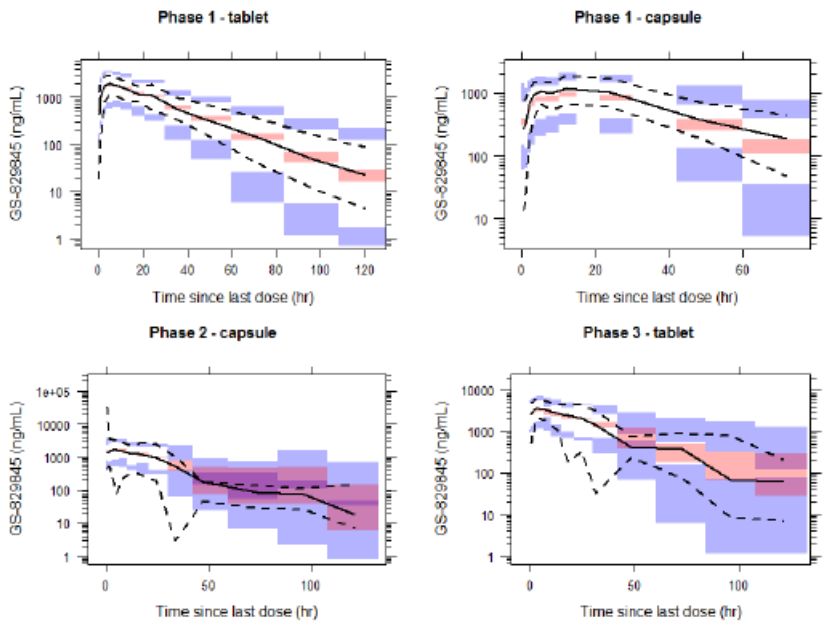
The final model of GS-829845

The structural popPK model that best described the GS-829845 data was a 1-compartment model, with first-order absorption and first-order elimination. Baseline creatinine clearance (bCLcr), bCRP, patient status, and SEXF were identified as statistically significant covariates on CL/F, whereas RA duration, baseline body weight (WT), and race as Asian were identified as statistically significant covariates on Vc/F. In addition, formulation was found to be significant impact F1. Final parameter estimates are presented in Table 9. The η-shrinkage for CL/F, Vc/F and ka was 15%, 61%, and 59% respectively. The ε-shrinkage was 10%.

Table 9. Comparison of GS-829845 Final Model Estimates, Bootstrap and SIR Results

Parameter	Parameter Description	Estimate [RSE[a]]	Bootstrap Estimate Median [2.5th and 97.5th Percentiles]	SIR Median [2.5th and 97.5th Percentiles]
θ1	Apparent oral clearance (L/h)	2.50 [0.8]	2.50 [2.46;2.54]	2.50 [2.46;2.54]
θ2	Apparent central volume (L)	81.3 [1.5]	81.3 [78.8;83.8]	81.2 [78.7;83.5]
θ3	Absorption rate constant (1/h)	0.478 [3.2]	0.478 [0.445;0.51]	0.478 [0.447;0.507]
θ6	Capsule effect on k_a	-0.222 [Fixed]	--	--
θ11	Capsule effect on F1	-0.133 [8.3]	-0.132 [-0.158;-0.109]	-0.134 [-0.155;-0.113]
θ7	CL_{cr} effect on CL/F (power)	0.339 [4.7]	0.339 [0.305;0.376]	0.338 [0.306;0.371]
θ8	CRP effect on CL/F (power)	-0.017 [20]	-0.017 [-0.0237;-0.0102]	-0.0171 [-0.0241;-0.0109]
θ9	HV effect on CL/F	0.147 [11.8]	0.147 [0.113;0.181]	0.147 [0.114;0.183]
θ10	Male effect on CL/F	0.0947 [14.2]	0.0951 [0.0644;0.123]	0.0941 [0.0689;0.122]
θ12	Asian race effect on V_c/F	0.163 [30.4]	0.163 [0.0632;0.267]	0.166 [0.07;0.267]
θ13	RA duration effect on V_c/F (power)	-0.0487 [24.7]	-0.048 [-0.0739;-0.0249]	-0.0469 [-0.0699;-0.0236]
θ14	Weight duration effect on V_c/F (power)	0.666 [9.8]	0.671 [0.507;0.805]	0.667 [0.538;0.797]
θ4	Proportional residual error	28% [0.8]	27.7 [26.9;28.5]	27.7 [27.2;28.1]
$\omega^2$11	Between subject variance on CL/F	24% [3.6]	23.6 [22.5;24.7]	23.7 [22.9;24.6]
$\omega^2$22	Between subject variance on V_c/F	26% [10.3]	26 [22.2;30.2]	26.5 [23.9;29.3]
$\omega^2$33	Between subject variance on k_a (slower)	64% [11.1]	63.6 [49.5;76.4]	63.7 [57.5;70.8]

CL/F = apparent oral clearance; CRP = C-reactive protein; IIV = interindividual variability; k_a = first-order absorption rate constant; PopPK = population pharmacokinetic; RSE = residual squared error; SIR = sampling importance resampling; V_c/F = apparent central volume.
Source: gs829845-gof-final-final-run030-20191231.R



CI = confidence interval; DV = observer concentrations; pcVPC = prediction-corrected visual predictive check.
The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles.
Source: gs829845-gof-final-final-run030-20191231.R

Figure 5. pcVPC of GS-829845 Plasma Concentration-Time Profiles Stratified by Phase and Formulation

Pharmacokinetics in target population

PK in the target population was similar to PK in healthy subjects, see PK parameters from phase 3 studies in Table 11.

Special population

Dose adjustments in general are based on the AUCeff, which is the AUC for the active moiety as the sum for the AUC of filgotinib and its active metabolite GS 829845, corrected for molecular weight and potency according to the following equation: AUCeff = AUCFIL + AUCmet * 1/10 * (425.51/357.43)

A threshold of 200% increase in AUCeff is considered for dose adjustments (*Table 10*).

Table 10. Effect of P-gp Inhibitors and Inducers and Special Populations on Effective AUC (AUC_{eff})

DDI or Special Population	Mean AUC_{eff} (%CV) (h•ng/mL)		% GLSM Ratio (90% CI)
	Test	Reference	Test/Reference
P-gp Inhibitor (Itraconazole) (n = 12)	6980 (14.4)	5899 (17.8)[a]	121 (115, 126)
P-gp Inducer (Rifampin) (n = 14)	10681 (17.6)	16194 (23.8)	66.6 (63.3, 70.1)
Moderate Hepatic Impairment (n = 10)	6381 (23.7)	5813 (44.7)	136 (76.2, 241)
Mild Renal Impairment (GFR 60 to < 90 mL/min) (n = 8)	6115 (35.9)	3937 (7.9)[b]	148 (101, 216)
Moderate Renal Impairment (GFR 30 to < 60 mL/min) (n = 8)	8008 (28.0)	3937 (7.9)[b]	196 (134, 286)
Severe Renal Impairment (GFR 15 to < 30 mL/min) (n = 2)	11895 (3.2)	3937 (7.9)[b]	303 (171, 537)

GLSM = geometric least squares mean; GFR = glomerular filtration rate; Study GLPG0634-CL-106 renal function groups based on absolute GFR (mL/min) using the Cockcroft-Gault (CG) equation.
$AUC_{eff} = AUC_{FIL} + AUC_{met} * 1/10 * (425.51/357.43)$
a n = 13
b n = 6

Impaired renal function (RI)

In an open, 2-part, 5-parallel-group design, subjects with varying degree of renal function received filgotinib 100 mg od for 10 days. Renal function was characterized using estimated using glomerular filtration rate (eGFR) by using the MDRD (modification of diet in renal disease) equation initially, before results based on absolute GFR were provided. Partly a reduced study design was applied, starting with investigations in severe RI (renal impairment) and then depending on the results mild and moderate RI were to be recruited

When using absolute GFR, comparable exposure of filgotinib was seen in mild RI and in subjects with normal renal function. The exposure of filgotinib was about 1.6 and 2.2-fold in moderate and severe RI compared in healthy subjects, respectively. The exposure of GS-829845 increased more than parent compound with decreasing degree of renal function, with a total exposure of about 1.4-fold in mild RI compared to normal and *ca* 3.5-fold in severe RI.

The AUCeff, which is determining for dose adjustments, was increased by 1.96-fold in patients with moderate renal impairment (*Table 10*).

Impaired hepatic function (HI)

Male and female subjects (n=48) diagnosed with different degrees of HI were included in an open, single dose study. Subjects were planned to be included in three cohorts, starting with cohort 1 (moderate HI). Adaptive cohorts 2 (severe HI) and 3 (mild HI) were to be enrolled as determined by review of preliminary data from cohort 1 to decide whether further evaluation in subjects with mild or severe HI was needed.

The exposure of filgotinib was about 1.6-fold and GS-829845 *ca* 1.2-fold in moderate HI compared to in healthy subjects. The metabolite/parent compound ratio was slightly less in HI compared to in healthy 17- and 22-fold, respectively. The $t_{1/2}$ was slightly increased in moderate HI 7.4 h compared to 5.5 h in healthy subjects.

Gender, Race, Age and Weight

All clinical studies were conducted in adult (≥18 years of age) patients or healthy volunteers.

Following filgotinib 200 mg once daily(od) for 10 days, in a randomized, placebo-controlled, study design, the PK of filgotinib and GS-829845 were investigated in healthy Japanese and Caucasian subjects (n=20). The PK of parent compound and major metabolite were in general comparable between the two groups with comparable AUCT, Cmax and renal excretion of unchanged compound but with a slightly longer t1/2 of filgotinib in Caucasians than in Japanese 11h and 7h.

There was a tendency to increasing exposure of both filgotinib and GS-829845 with age following filgotinib 100 mg od. The AUC0-24h was about 1.4-fold in subjects ≥75 years compared to in 40-50 years subjects. The t1/2 was ca 6h independently of age. CLR (renal clearance) of both filgotinib and GS-829845 decreased with age.

There is a trend between the AUC of filgotinib and weight (majority of subjects weighed between 60-100 kg). However, the trend is not considered to be clinically relevant. There does not appear to be a clear trend between AUC of GS-829845 and weight. The relationship should be re-evaluated for both compounds if patients weighing less are included.

Table 11 Elderly population enrolled in clinical trials

	Age 65-74 (Older subjects number / % of total number)	**Age 75-84 (Older subjects number / % of total number)**	**Age 85+ (Older subjects number /% of total number)**
PK Trials	430 (15%)	92 (3%)	2 (< 1%)

Total 2862 subjects in demographic population PK analysis set from phase 2 and 3 studies

Population PK model

The demographic factors baseline age, baseline body weight (WT), sex, and race (White vs Black or African American vs Asian, and Other) were assessed as covariates on filgotinib PK parameters, however, the analysis is considered inadequate and no conclusion can be made based on this analysis.

Interactions

The interaction potential of filgotinib/GS-829845 has been tested in a number of *in vitro* and some *in vivo* studies. The calculated cut-off values (according to EMA DDI guideline) used in the interpretation of *in vitro* data to predict potential interactions *in vivo* following recommended 200 mg od were for filgotinib:

C_{max} (µM)	f_u (%)	$50xC_{max,u}$ (µM)	25xInlet $C_{max,u}$ (µM)	0.1xdose/250 ml (µM)
6.1	45	168	488	188

and for GS-829845 $50xC_{max,u}$=274 µM.

Enzymes

Substrate

- Filgotinib is a substrate of CES2, CES1b and CES1c

Perpetrator

- A ca 25% inhibition was seen *in vitro* at highest concentration of filgotinib tested - for CYP1A2 and 3A4/5 at 70 µM and for CYP2A6 at 106 µM
- GS-829845 inhibited CYP2C9 and CYP2C19 by ca 50% and 40%, respectively, *in vitro* at clinically relevant concentration, with AUCR values of 1.05 using the mechanistic static model, suggesting no significant interaction
- *In vitro* signals on induction of CYP2B6, 3A and 1A2 at filgotinib 10 µM

Transporters

Substrate

- Filgotinib and GS-829845 are Pgp substrates
- GS-829845 is a breast cancer resistance protein (BCRP) substrate

Perpetrator

- Filgotinib and GS-829845 inhibited OATP1B1 *in vitro* with IC50 of 110 µM and 90 µM, respectively and OATP1B3 with IC50 of 168 µM and 158 µM, respectively
- Filgotinib inhibited *in vitro* OCT1 (IC50=152 µM), OCT2 (IC50=9 µM), OCT3 (IC50=188 µM), MATE1 (IC50=9 µM) and MATE2-K (IC50=5 µM)
- GS-829845 inhibited OCT2 and MATE2-K *in vitro* with IC50 of 15 µM and 11 µM, respectively
- Filgotinib inhibited OAT3 *in vitro* with IC50 of 90 µM, but did not inhibit OAT1 *in vitro* (IC50>321 µM)
- in vitro data of inhibition of PgP and BCRP by GS-829845 is inconclusive

In vivo

- No relevant difference in the PK of filgotinib was seen following co-administration with omeprazole (PPI) or famotidine (H2RA) - thus the absorption did not change due to increased pH in the GI-tract
- Co administration of filgotinib and an oral contraceptive ethinylestradiol/levonorgestrel did not result in any change of exposure of EE or LNG - thus no indication of induction of CYP3A (also supported by the *in vivo* midazolam data) or UGT by filgotinib
- *In vivo* DDI study with metformin (known OCT2, OCT1/3, MATE1/2K substrate) showed comparable exposure independently if dosed alone or together with filgotinib – thus no inhibition of the transporters by filgotinib
- Coadministration of filgotinib with rifampicin (600 mg od, a prototypical P-gp inducer) showed a slightly lower exposure of filgotinib and GS-829845 compared to when filgotinib was dosed alone (0.73- and 0.62-fold, respectively). This decrease in active moiety is not deemed clinically relevant.
- *In vivo* DDI study with itraconazole inhibited Pgp marginally resulting in an exposure of 1.4-fold for filgotinib
- *In vivo* DDI study (PK-sub-study in CL-202) with methotrexate (substrate for OAT1 and OAT3) showed no major impact on methotrexate exposure when dosed with filgotinib.
- *In vivo* PK sub-study in GS-US-417-0303 indicate no effect on filgotinib or GS-829845 exposure by methotrexate.

Conclusions – DDI

Enzymes

CYP3A: - *in vitro* signals of inhibition and induction by filgotinib

- no indication of inhibition/induction *in vivo* DDI with midazolam (filgotinib od for 8 days)

CYP1A2: - *in vitro* signals of inhibitionand induction by filgotinib

CYP2C9 and CYP2C19:

- *in vitro* inhibition by GS-829845, in vivo relevance ruled out based on the mechanistic static model

CYP2B6: - *in vivo* induction cannot be ruled out based on *in vitro* data

CYP1A6: - *in vitro* inhibition by filgotinib – not mandatory to study

Transporters

P-gP and BCRP: -inconclusive *in vitro* results of inhibition by GS-829845

OATP1B1 and OATP1B3:

- *in vitro* signals of inhibition by filgotinib and GS-829845

- should be verified *in vivo* or *in silico* meanwhile SmPC restrictions

Exposure relevant for safety evaluation

The exposures relevant for safety evaluation were the following: Cmax 2643 ng/mL and AUCtau 7048 ng·h/mL for filgotinib, and Cmax 3490 ng/ml and AUCtau 72600 ng·h/mL for GS-829845.

2.4.3. Pharmacodynamics

Mechanism of action

Filgotinib is an ATP-competitive and reversible inhibitor of the JAK family. There are currently three approved JAK-inhibitors and the knowledge on the effects and side effects are becoming increasingly known. Please refer to the non-clinical assessment for further characterisation of the MoA for filgotinib (Section 2.3.).

Primary and Secondary pharmacology

Relationship between plasma concentration and response

Data

Estimated filgotinib and GS-829845 exposures were derived using the population PK model.

As both filgotinib and its metabolite, GS-829845, contribute to efficacy, their exposures were combined into a single parameter, AUCeff. AUCeff was defined as the weighted sum of steady-state AUC0-24 values

of filgotinib and GS-829845 based on a relative 10-fold potency on JAK1 inhibition for filgotinib over the metabolite and molecular weight.

The exposure-response analyses for safety were based on the pooled population in Phase 2/3 studies and were performed separately for filgotinib and GS-829845 to characterize the individual safety profiles of each analyte.

Results

Graphical analysis of exposure-efficacy and exposure-safety was conducted.

Exposure-efficacy analysis (American College of Rheumatology (ACR) responses stratified by octiles of AUCeff in subjects with RA) across the Phase 3 program confirmed that filgotinib produced robust therapeutic effects across the exposure range observed at both 200 mg and 100 mg once daily (See Figure 6).

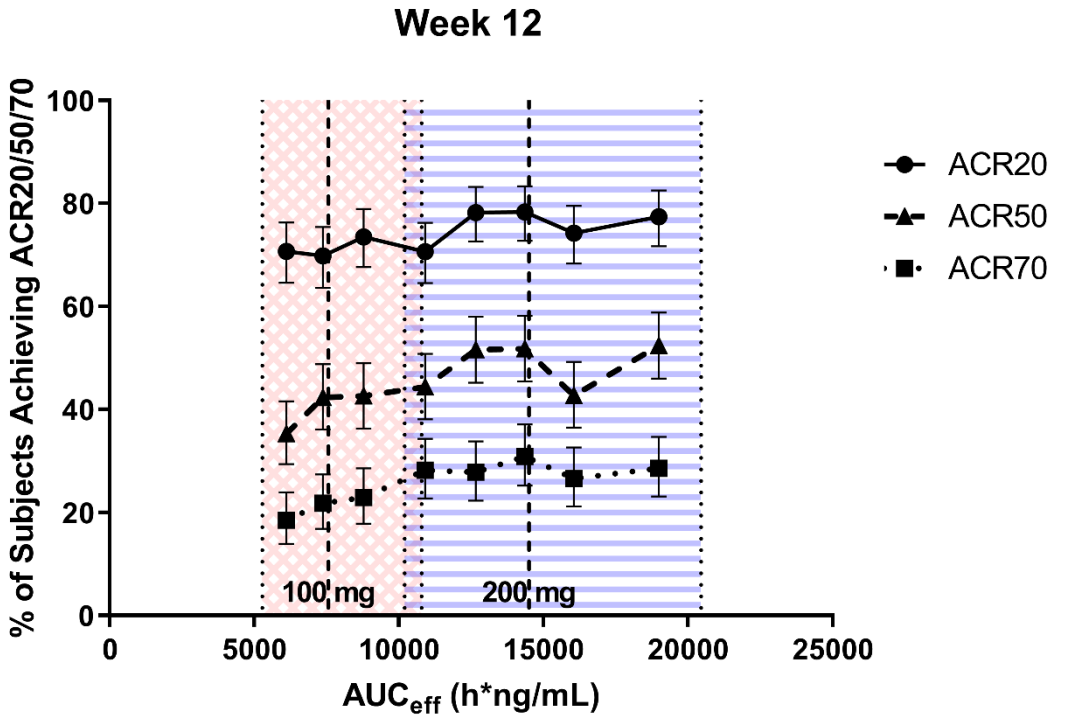


Figure 6 Exposure Response Relationship of AUCeff Based on Filgotinib and GS 829845 Against ACR Responses at Week 12 Following Once Daily Dosing of Filgotinib 100 mg and 200 mg in Subjects with RA (Filgotinib and GS 829845 PK/PD Analysis Set in Pooled Phase 3 Studies)

PK/PD analysis set includes subjects with RA who were enrolled/randomized, received at least 1 dose of filgotinib in studies GS-US-417-0301, GS-US-417-0302, and GS-US-417-0303, and had at least 1 nonmissing PK parameter of interest.

Each symbol represents the proportion of subjects achieving the ACR response with the vertical line showing the 95% confidence interval within each group based on the Clopper-Pearson method. Circles show ACR20, triangles show ACR50, and squares show ACR70. Shaded areas with blue stripes show median (dashed vertical line) and fifth and 95th percentiles (dotted vertical lines) of AUCeff for filgotinib 200 mg once daily in Phase 3 subjects with RA; shaded areas with pink cross pattern show median (dashed vertical line) and fifth and 95th percentiles (dotted vertical lines) of AUCeff for filgotinib 100 mg

once daily in Phase 3 subjects with RA. AUCeff is based on the population PK-predicted exposure in Phase 3 subjects with RA receiving filgotinib.

Exposure-safety analysis by serious adverse events (SAEs) and serious infections was generated. Exposure-adjusted incidence rates (EAIR) of SAEs and serious infections based on safety data up to 52 weeks are stratified by octiles of AUC0-24 (x-axis). The analysis included population PK-based exposure estimated AUC0-24, with the upper 4 octiles approximately corresponding to a 200 mg once-daily dose and the lower 4 octiles associated with a 100 mg once-daily dose.

In the analysis, subjects with higher PK exposures (upper 4 octiles) showed similar and overlapping EAIR of SAEs compared with subjects with lower PK exposures (lower 4 octiles) for both filgotinib and GS-829845. Similarly, EAIR of serious infections highly overlapped regardless of the higher or lower PK exposures. Thus, no exposure-driven trends are present, indicating a lack of association between filgotinib or GS-829845 exposures and SAEs or serious infections.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Filgotinib is a small molecule with no chiral centre and is very insoluble at physiological pH (BSC2). The major elimination pathway is metabolism to one major metabolite GS-829845, the systemic plasma concentration of GS 829845 was ca 15-fold compared to the exposure of filgotinib following oral administration with recommended doses. The *in vitro* activity of GS-829845 is about 1/10 of the activity of filgotinib, thus active moiety should be considered when risks with interactions or decreased organ function are discussed.

Bioanalytical assays using LC-MS/MS for determination of filgotinib and the major metabolite GS 829845 in plasma as well as in the urine have been developed. The assays have been appropriately validated/qualified for their intended purpose.

Formulation development has been ongoing during the whole development also during the late phase, the initial phase-3-formulation was modified/adjusted. Relative bioavailability studies have shown that the capsule (filgotinib-HCl) used in the program cannot be claimed BE to the "early tablet"/phase-1 tablet (filgotinib-HCl). The "early tablet" 100 mg*2 is BE to the "new tablet" (filgotinib maleate) 200 mg. The "new tablet" and the commercial tablet differ only in their qualitative composition, which is not expected to have an impact on PK. Thereby, the lack of an additional BE study for the commercial tablet is acceptable to CHMP.

The unbound fraction (fu) of both filgotinib and GS-829845 are important to know in the evaluation of systemic exposure in different situations as eg organ impairment. One-point estimations of fu at non-clinically relevant concentrations have been reported and further *in vitro* data were requested. The Applicant referred to *in vivo* protein binding data to justify the lack of further *in vitro* testing, which was deemed acceptable to CHMP.

High exposure of GS-829845 was seen after both single and repeated dosing. In the SAD/MAD study the exposure of GS-829845 at steady state was about 20-fold compared to filgotinib but decreased with dose from 24- to 18-fold at doses from 25 to 100 mg bid. The exposure ratio between main metabolite and parent compound was 16-fold after 200 mg od. A fairly dose-proportional increase in exposure was seen at doses <100 mg but a more than dose-proportional increase at doses of ≥100 mg. The Applicant presented data showing that both filgotinib and GS-829845 exhibit time-independent PK.

Filgotinib can be administered with or without food.

The major elimination pathway for filgotinib is via metabolism to GS-829845, with ca 80% of the dose excreted as GS-829845 or further conjugation. The overall *in vitro* metabolic turnover in hepatocytes was low but GS-829845 was formed during *in vitro* incubations with recombinant CES (carboxylesterases). The presented data demonstrates that filgotinib is primarily a substrate of CES2 and that CES1 has a minor involvement in the metabolism of filgotinib. Polymorphism of CES was likely to have a minimal impact on the PK of filgotinib, which is acceptable. There is however a difference between the inhibition of filgotinib metabolism by the pan inhibitor of amidases and esterases BNPP, as compared to the inhibition by the CES2 inhibitor only. Other amidases than CES2, CES1b and CES1c were however not studied in this system. It can currently not be concluded whether it is truly only CES1 and CES2 that are responsible for the metabolism of filgotinib to GS-829845, or whether other enzymes, also inhibited by the pan inhibitor of amidases and esterases BNPP, may be involved. As the Applicant noted, no clinical inhibitors of other amide hydrolases are reported; therefore, the issue was not further pursued by CHMP.

The Applicant discussed the clinical relevance of CES inhibition, noting that it is unclear whether loperamide concentrations high enough to inhibit CES2 may occur *in vivo*. While the applicants concern regarding the clinical relevance of the interaction with loperamide is acknowledged, this elimination pathway is responsible for 80% of the elimination of filgotinib, which may result in significant increased exposure if this pathway was inhibited. There are however other examples of stronger CES2 inhibitors in the literature, even if they have only been studied *in vitro*. As this uncertainty remains, the CHMP requested the MAH to include a warning for co-administration with CES2 inhibitors in section 4.5 of the SmPC. Given the lower involvement of CES1, the CHMP agreed that no warning is required for CES1 inhibitors.

The Applicant clarified that dose adjustments are proposed based on the active moiety exposure (AUCeff) and not solely on the exposure of filgotinib. AUCeff is the sum of AUCs (as calculated by NCA) of filgotinib and GS 829845, corrected for their molecular weight and for the potency of GS 829845 (1/10). AUCeff is not corrected for the respective protein binding of filgotinib and GS 829845, which is acceptable, since these are in the same range. The proposed approach is endorsed by the CHMP. The defined threshold for a dose adjustment (200%) required further discussion, as adequate safety data was not provided for moderate renal impairment, where a 196% increase of AUCeff is observed and a dose adjustment in this population was included upon CHMP request in the SmPC.

Instead of performing a new *in vitro* experiment on P-gp and BCRP inhibition by GS-829845 as requested by the CHMP, the Applicant recalculated the inhibitory effect of GS-829845 using different equations from the literature. There are however still uncertainties remaining regarding the initial experiment where inconsistent patterns are seen over the studied concentration range rendering the experiment unreliable, and the maximal studied concentration was far below the cutoff. As a consequence, the Section 4.5 of the SmPC was updated by the Applicant to state that "*in vitro* studies are inconclusive regarding the potential of the primary metabolite of filgotinib GS 82984 to inhibit P-gp or BRCP. *In vivo* inhibition of these transporters cannot be excluded, and caution is recommended when substrates with a narrow therapeutic index (e.g. digoxin) are co-administered with filgotinib". At the CHMP's request, the applicant has committed to perform a new *in vitro* study of the inhibition of P-gP and BCR by GS-829845, with concentrations at least up to 50xCmax,u=274 µM by December 2020. If the outcome of the study is negative, the SmPC may be updated. Should the study result in inconclusive data, a second *in vitro* system should be considered.

The mechanistic static model was used by the Applicant to verify the *in vitro* signals on CYP2C9 and CYP2C19 inhibition by GS 829845, with Ki determined from two experiments. The resulting AUR is below the guideline cut-off. Thus GS-829845 is not likely a clinically relevant inhibitor of CYP2C9 or CYP2C19.

The inhibition of OATP1B1 and OATP1B3 has not been verified *in vivo* instead the Applicant has developed and used a preliminary physiologically-based pharmacokinetic (PBPK) model (SimCYP v.18, Certara UK)

to predict the potential for filgotinib and GS-829845 to inhibit OATP1B1 and OATP1B3. A qualification of the PBPK platform for the intended purpose has been presented, however key elements to qualify the model are missing. Therefore, the applicant was requested to include a warning for co-administration with OATP1B1 and OATP1B3 substrates in section 4.5 of the SmPC. The applicant has also committed to the post authorisation measure to perform a clinical DDI study to investigate OATP1B1 and OATP1B3 inhibition by filgotinib and GS-829845 with the proposed timeline for the submission of new clinical DDI data by September 2022.

From a mechanistic point of view there appears to be a limited potential for interactions between filgotinib, GS-829845 and most of the different cDMARDs. However, there are still some uncertainties regarding both filgotinib and GS-829845 as perpetrators. With the updated indication (see Section 2.5), only methotrexate is to be used in combination with filgotinib. Regarding methotrexate all data; mechanistic discussion, *in vitro* as well as *in vivo* data, point to no potential interaction between filgotinib and methotrexate. Hence, a new dedicated *in vivo* DDI study between methotrexate and filgotinib was not considered warranted by the CHMP.

There was no effect of filgotinib on the PK of the combined contraceptive ethinyl estradiol and levonorgestrel when co administered with filgotinib; thus no dose adjustment of oral contraceptives is required. *In vitro* studies are inconclusive regarding filgotinib's potential to induce CYP2B6 or CYP1A2. However, *in vivo* induction cannot be excluded. This information is adequately reflected in the SmPC.

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

No clinically relevant changes in the exposures (AUC) of filgotinib and GS 829845 individually, or their combined exposure (AUCeff), were observed in subjects with moderate hepatic impairment (Child Pugh B). Hence, 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.

The pharmacokinetics of filgotinib and GS 829845 were unaffected in subjects with mild renal impairment (CrCl 60 to < 90 mL/min). Hence, no dose adjustment is required in patients with mild renal impairment (creatinine clearance [CrCl] $\geq$ 60 mL/min).

Increases in exposures (AUC) of filgotinib, GS 829845, and combined AUCeff ($\leq$ 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 AUCeff. Hence, 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).

The pharmacokinetics of filgotinib has not been studied in subjects with end stage renal disease (CrCl < 15 mL/min); hence, filgotinib is not recommended for use in these patients.

See also safety section 2.6.

The Applicant conducted population PK analysis with the objectives to characterize the PK of filgotinib and GS-829845, determine the effects of intrinsic and extrinsic factors on the PK of filgotinib and GS-829845 to better understand clinical factors that might affect exposure in individual subjects, and to provide model predicted individual subject PK parameter estimates from PopPK models for exposure-response analysis. There are identified issues in all aspects concerning the model, i.e. the handling of data, the structural and statistical model, and the covariate analysis. The popPK analysis is considered inadequate and no conclusion can be made based on this analysis with regard to demographic factors. The model

cannot adequately capture phase 1 data, not Cmax of phase 2 or phase 3 data. Trends are observed in the goodness-of-fit plots. The filgotinib and GS-829845 models are considered inadequate and should not be used for determining the effect of intrinsic and extrinsic factors on the PK of filgotinib and GS-829845, or for predictions or simulations. The models can estimate the observed phase 2 and phase 3 AUC for filgotinib and GS-829845 sufficiently in this application for investigation of possible trends between AUC and efficacy and safety.

Pharmacodynamics

As both filgotinib and its metabolite , GS-829845, contribute to efficacy, their exposures were combined into a single parameter, AUCeff. The exposure-response analyses for safety were based on the pooled population in Phase 2/3 studies and were performed separately for filgotinib and GS-829845 to characterize the individual safety profiles of each analyte. This approach (combining concentration for efficacy assessment) is acceptable to the CHMP. The population PK model was used to predict individual exposures of filgotinib and GS-829845, which were then used in the evaluation of the relationships (exposure-response). With regard to AUCeff versus ACR20/50/70 it appears that the patients have reached an effect plateau with the 200 mg dose. There does not seem to be an association between filgotinib or GS 829845 AUC and SAEs or serious infections.

2.4.5. Conclusions on clinical pharmacology

The PK of filgotinib have been adequately described. Polypharmacy is expected in the target population and some additional DDI data will have to be provided as post-approval measure to predict potential PK interactions in the clinical setting.

A starting dose of 100 mg once daily is recommended for patients aged 75 years and older as clinical experience is limited.

No dose adjustment is required in patients with mild renal impairment (creatinine clearance [CrCl] $\geq$ 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.

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.

The population PK model is considered inadequate for assessment of impact of intrinsic and extrinsic factors and simulation. The models can estimate the observed phase 2 and phase 3 AUC for filgotinib and GS-829845 sufficiently in this application for investigation of possible trends between AUC and efficacy and safety.

Overall, the application is acceptable from a clinical pharmacology perspective.

2.5. Clinical efficacy

General features of submitted data and sought indication

The efficacy of filgotinib were evaluated in 5 Phase 2 studies in an MTX-IR population (Studies GLPG0634-CL-201, GLPG0634-CL-202, GLPG0634-CL-203, GLPG0634-CL-204, and the long-term extension study GLPG0634-CL-205 [DARWIN 3]) and Phase 3 studies in a MTX-IR population (Study

GS-US-417-0301), in a bDMARD-IR population (Study GS-US-417-0302), in an MTX-naive population (Study GS-US-417-0303), and a long-term extension (LTE) study (Study GS-US-417-0304 [FINCH 4]), see *Table 12*.

The duration of FINCH 2 was 24 weeks while the other two-phase III studies were of 52 weeks duration. In the initial submission, only data up to 24 weeks were included (in 24 week-CSRs). As a response to the Day 120 list of question (LoQ0, the final CSRs with week 52-data were provided.

For the three Phase 3 RCT, the primary analysis consisted of a superiority test of filgotinib based on the ACR20 response rate (at week 12 in FINCH 1,2 and at week 24 in FINCH 3) with an NRI-approach.

There was one additional Phase 2 study in subjects with RA (Study GS-US-379-1582) that included a cohort of 21 subjects who received filgotinib 200 mg for 12 weeks (considered as an exploratory group in the study). According to the Applicant, study GS-US-379-1582 was an exploratory study conducted in parallel to Phase 3; therefore, it was not used to support dose selection (although an effect of filgotinib vs placebo was noted).

Table 12: Studies Supporting the Clinical Efficacy and Safety for Filgotinib for Rheumatoid Arthritis

Study	Study Design	Treatment Regimens	Number of Subjects[a]	Subject Population
GS-US-417-0301 (FINCH 1)	Phase 3, randomized, double-blind, placebo- and active-controlled study	Filgotinib 200 mg, QD; filgotinib 100 mg, QD; adalimumab 40 mg SC, Q2W; or placebo for up to 52 weeks. Subjects were on a stable dose of 7.5 to 25 mg MTX/week.	1755	Adult subjects with moderately to severely active RA; MTX-IR
GS-US-417-0302 (FINCH 2)	Phase 3, randomized, double-blind, placebo-controlled study	Filgotinib 200 mg, QD; filgotinib 100 mg, QD; or placebo for up to 24 weeks. Subjects were taking a stable dose of 1 to 2 permitted csDMARDs.	448	Adult subjects with moderately to severely active RA; bDMARD-IR
GS-US-417-0303 (FINCH 3)	Phase 3, randomized, double-blind, placebo- and active-controlled study	Filgotinib 200 mg QD and MTX up to 20 mg QW; filgotinib 100 mg QD and MTX up to 20 mg QW; filgotinib 200 mg QD; or MTX up to 20 mg QW for up to 52 weeks	1249	Adult subjects with moderately to severely active RA; MTX-naive
GS-US-417-0304 (FINCH 4)	Phase 3, double-blind, long-term-extension study	Filgotinib 200 mg QD or filgotinib 100 mg QD for up to 6 years	1230	Eligible subjects who had completed 1 of the 3 parent RA studies[c] (GS-US-417-0301, GS-US-417-0302, or GS-US-417-0303)
GLPG0634-CL-201	Phase 2a, randomized, double-blind, placebo-controlled study	Filgotinib 200 mg QD; filgotinib 100 mg BID; or placebo for up to 4 weeks Subjects were on a stable dose of 7.5 to 25 mg MTX/week.	36	Adult subjects with active RA; MTX-IR
GLPG0634-CL-202	Phase 2a, randomized, double-blind, placebo-controlled, add-on study	Filgotinib 30 mg QD; filgotinib 75 mg QD; filgotinib 150 mg QD; filgotinib 300 mg QD; or placebo QD for up to 4 weeks Subjects were on a stable dose of 7.5 to 25 mg MTX/week.	91	Adult subjects with active RA; MTX-IR
GLPG0634-CL-203 (DARWIN 1)	Phase 2b, randomized, double-blind, placebo-controlled, dose-finding, add-on study	Filgotinib 25 mg BID; filgotinib 50 mg QD; filgotinib 50 mg BID; filgotinib 100 mg QD; filgotinib 100 mg BID; filgotinib 200 mg QD; or placebo BID for up to 24 weeks Subjects were on a stable dose of 15 to 25 mg MTX/week.	Total: 594 Pooled Phase 2/3 Safety Population: 276[b]	Adult subjects with moderately to severely active RA; MTX-IR
GLPG0634-CL-204 (DARWIN 2)	Phase 2b, randomized, double-blind, placebo-controlled, monotherapy, dose-finding, study	Filgotinib 50 mg QD; filgotinib 100 mg QD; filgotinib 200 mg QD; or placebo QD for up to 24 weeks	Total: 283 Pooled Phase 2/3 Safety Population: 226[b]	Adult subjects with moderately to severely active RA; MTX-IR
GLPG0634-CL-205 (DARWIN 3)	Phase 2, open-label, multicenter, long-term extension study	Filgotinib 200 mg QD, filgotinib 100 mg BID, or filgotinib 100 mg QD (US males) for approximately 96 months Subjects could be switched to filgotinib 100 mg QD when deemed necessary by the investigator. Subjects may have been on a stable dose of MTX.	Total: 739 Pooled Phase 2/3 Safety Population: 487[b]	Eligible subjects who had completed 1 of the 2 parent RA studies (GLPG0634-CL-203 or GLPG0634-CL-204)

bDMARD = biologic disease-modifying antirheumatic drug; BID = twice daily; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CSR = clinical study report; IR = inadequate responder; MTX = methotrexate; Q2W = twice weekly; QD = once daily; QW = once weekly; RA = rheumatoid arthritis; SC = subcutaneous; US = United States

a. Safety data through 08 October 2018 are summarized for ongoing studies GS-US-417-0301, GS-US-417-0303, and GS-US-417-0304. For ongoing study GLPG0634-CL-205, safety data through 30 May 2018 are summarized.
b. Subjects in Studies GLPG06343-CL-203, GLPG06343-CL-204, and GLPG06343-CL-205 who received filgotinib 200 mg once daily, filgotinib 100 mg once daily, or placebo (±MTX) were included in the Pooled Phase 2 and Phase 3 Safety Analysis Set.
c. Subjects who discontinued blinded study drug in GS-US-417-0302 due to inadequate response of their RA were allowed to be enrolled into GS-US-417-0304.

Source: GS-US-417-0301 Interim Week 24 CSR; GS-US-417-0302 CSR; GS-US-417-0303 Interim Week 24 CSR; GS-US-417-0304 Interim CSR; GLPG0634-CL-201 CSR; GLPG0634-CL-202 CSR; GLPG0634-CL-203 CSR; GLPG0634-CL-204 CSR; GLPG0634-CL-205 Interim CSR

The indication initially proposed by the Applicant encompasses monotherapy and combination with MTX ≥ second line.

2.5.1. Dose response study(ies)

Design and conduct of phase II studies

Two completed 4-week Phase 2a studies; GLPG0634-CL-201 and GLPG0634-CL-202, explored once or twice daily filgotinib doses, on top of MTX, up to a total daily dose of 200 mg or 300 mg, respectively. Doses above 200 mg daily were not pursued in Phase 2b because an exposure-response analysis was considered to demonstrate that responses were at plateau with the 200-mg daily dose.

The phase 2b studies GLPG0634-CL-203; DARWIN 1 and GLPG0634-CL-204; DARWIN 2 included subjects exposed at 3 different daily doses of GLPG0634 i.e. filgotinib (i.e. 50, 100, and 200 mg daily) at 2 dose regimens (once and twice daily administration). Both studies - the first MTX-add on, the second monotherapy - were to be conducted in the second line, MTX-IR population and were randomized, double-blind and placebo-controlled, with ACR 20 at week 12 being the primary endpoint and an NRI-approach. Regarding DARWIN 2, it is noted that although this was considered as a monotherapy study, antimalarial DMARDs were included among the permitted medications.

Data from the phase II studies

In GLPG0634-CL-201, 36 MTX-IRs subjects were randomized. At Week 4, the number and percentage of ACR20 responders (the primary efficacy endpoint) was 4 (33.3%), 9 (75.0%), and 11 (91.7%) in the placebo, Filgotinib 200 mgx1 and the Filgotinib 100 mgx2 groups, respectively.

In GLPG0634-CL-202, 91 MTX-IRs subjects were randomized and received study treatment. At Week 4, the percentage of subjects achieving ACR20 response (the primary endpoint) in the placebo group was 41.2% and in the Filgotinib 30 mg/day, Filgotinib 75 mg/day, Filgotinib 150 mg/day and Filgotinib 300 mg/day groups: 35.3%, 54.5%, 40.0%, and 65.0%, respectively.

In GLPG0634CL203; DARWIN 1, 594 subjects were randomized and treated. The outcome of the primary endpoint, ACR 20 response at week 12, was: 44.2% in the placebo group, 56.1% in 50 mgx1 group, 63.5% in the 100 mgx1 group, 68.6% in the 200 mgx1, 57.0% in the 25 mgx1 group, 60.0% in the 50 mgx2, 78.6% in the 100 mgx2 group (p-values<0.05 for the comparison vs placebo for the 100 mgx1, 200 mgx1 and 100 mgx2 groups). Dose-dependent responses were observed in the majority of these secondary efficacy parameters including proportion of subjects achieving remission/Low Disease Activity (LDA).

In GLPG0634-CL-204; DARWIN 2, 283 subjects were randomized and treated. The outcome of the primary endpoint, ACR 20 response at week 12, was: 29.2% in the placebo group, 66.7% in the 50 mgx1 group, 65.7% in the 100 mgx1 group and 72.5% in the 200 mgx1 group (p<0.0001 for all comparisons vs placebo). The outcome for the secondary endpoint Disease Activity Score 28 C-reactive protein (DAS28 [CRP]) remission or LDA at Weeks 12 (NRI [ITT Population]) was as follows at week 12: 13.9% in the placebo group, 23.6% in the 50 mgx1 group, 27.1% in the 100 mgx1 group and 44.9% in the 200 mgx1 group (p-value<0.05 for the comparison of the 200 mg group vs placebo). At week 24 the proportion with DAS28 (CRP) remission or LDA was 34.7% in the 50 mgx1 group, 50.0% in the 100 mgx1 group and 42.0% in the 200 mgx1 group.

Following the phase II studies, the Applicant had initially selected only the 200 mgx1 dose to be tested in the phase 3 programme. As this was questioned by the SAWP/CHMP, both the 100 mg once daily and 200 mg once daily-doses were then ultimately chosen for the phase 3 studies.

From the week 156- interim CSR of GLPG0634-CL-205; DARWIN 3, the long term follow-up that included subjects that received filgotinib monotherapy (n = 242, rolled over from parent study DARWIN 2) or filgotinib with MTX (n = 497, rolled over from parent study DARWIN 1), there are indications that the treatment effect of filgotinib (as monotherapy or in combination with MTX) is maintained for up to 3 years in patients. It is noted that 229/491 MTX-IR subjects in the MTX + Filgotinib group had low disease activity at baseline and 200/290 subjects had low disease activity at week 156. For the monotherapy group, the numbers were 97/234 and 88/136. The majority of subjects were on 200 mg Filgotinib/day.

2.5.2. Main study(ies)

FINCH 1 (GS-US-417-0301): A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 weeks in Combination with Methotrexate to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate

Methods

Study Participants and Treatments

FINCH 1 is a placebo and active-controlled MTX-add on study that included a second line population (active RA despite MTX-treatment) with poor prognostic factors that were randomized to either Filgotinib 100 mgx1, Filgotinib 200 mgx1, the TNF-inhibitor adalimumab or placebo, with a rescue-possibility to standard of care (SOC) at week 14 (in case at least 20% improvement from baseline in swollen joint count=SJC and tender joint count=TJC had not been achieved). In addition to MTX, concomitant anti-malarial csDMARDs were allowed but no other csDMARDs.

At Week 24, all subjects assigned to placebo were reassigned to either filgotinib 100 mg once daily or 200 mg once daily in a blinded fashion and continued in the study through Week 52. All subjects who continued on study drug were evaluated for loss of therapeutic response from Week 30 through Week 52. Subjects failing to maintain at least a 20% improvement from baseline in TJC and SJC discontinued from investigational study drugs but continued in the study. All subjects meeting this criterion are to receive standard of care RA treatment are not eligible for enrolment in the separate LTE -study; FINCH 4.

Objectives

Primary objective

To evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving an American College of Rheumatology 20% improvement response (ACR20) at Week 12 (superiority hypothesis).

Outcomes/endpoints

The primary endpoint was the proportion of subjects who achieved an ACR20 response at Week 12.

The key secondary efficacy endpoints (according to protocol and statistical analysis plan (SAP) 2) were: The proportion of subjects who achieve DAS28 (CRP)≤3.2 (=LDA) at Week 12, Change from Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 12, The proportion of subjects who achieve DAS28 (CRP)<2.6(=remission) at Week 24, Change from Baseline in modified total Sharp scores (mTSS) at Week 24.

Primary and key secondary endpoints were also measured at time points up to Week 24. Additional endpoints measured over time included ACR50/70 response rates and changes in individual ACR components, other composite measures of disease activity, EULAR response criteria, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and additional patient-reported outcomes.

Statistical methods, randomisation and blinding

Overall, 1650 subjects were planned to be randomised in a 3:3:2:3 ratio to receive filgotinib 200 mg (450), filgotinib 100 mg (450), adalimumab (300), or placebo (450) using an Interactive Web Response System (IWRS). Randomisation was stratified by geographic region (group A to E), prior exposure to bDMARD (Yes or No), and presence of RF or anti-CCP Ab at screening (Yes or No). Masking was to be achieved by the use of filgotinib and adalimumab matching placebos and double-dummy technique. The sample size was driven by the key secondary endpoint, change from baseline in mTSS at Week 24 which implied a high power for the analysis of the primary endpoint (>90%). The sample size estimation also considered the non-inferiority comparison with adalimumab aiming at demonstrating that filgotinib 200 mg preserves more than 50% of the effect of adalimumab with respect to the response rate of DAS28(CRP) ≤ 3.2 at Week 12.

The geographic regions in FINCH 1 was:

- Group A: Australia, Belgium, Canada, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Republic of Korea, South Africa, Spain, United Kingdom, and USA
- Group B: Bulgaria, Czech Republic, India, Romania, Russian Federation, Slovakia, Ukraine, Serbia, Hungary, and Poland
- Group C: Argentina and Mexico
- Group D: Hong Kong, Taiwan, and Thailand
- Group E: Japan

A planned Week 24 analysis was conducted after all subjects had either completed their Week 24 visit or prematurely discontinued from the study. A prespecified sponsor team, including members who were not actively involved in the conduct of the study after unblinding, reviewed the Week 24 unblinded efficacy analysis results and the safety results up to the data-cut of 08 October 2018.

Statistical methods were described in two SAPs based on differences in feedback from regional health authorities. SAP 2 was based on the analysis hierarchy specified in the protocol consistent with CHMP Scientific Advice. SAP 2 (version 1.0 (EMA)) was dated 05 February 2019 and was finalised before the unblinding of Week 24 analysis.

Two estimands were defined; a composite estimand and a treatment-policy estimand with the former considered primary. Intercurrent events where defined as intake of SOC medications due to inadequate response, study treatment discontinuation and study discontinuation. For the primary composite estimand the occurrence of an intercurrent event was taken to be a component of the variable, implying e.g. that an ACR20 responder besides a successful clinical outcome was required not to have discontinued

randomised treatment or needing rescue/SOC. With the two estimand strategies analyses were based on two data sets; in primary analyses the data set comprised only data collected while the subject was on randomised treatment ignoring any data collected after the occurrence of an intercurrent event. For secondary analyses, the data set comprised all available data i.e. also measurements observed after a subject had discontinued randomised treatment but stayed in the study on SOC (instead ignoring the occurrence of an intercurrent event). Analyses using both approaches were planned and have been performed for the primary as well as key secondary endpoints.

For categorical endpoints, including the primary (ACR20) and e.g. DAS28(CRP) endpoints, a logistic regression analysis with treatment groups and stratification factors in the model was used for statistical inference. For e.g. ACR20, the non-stratified response rate difference along with corresponding 95% CI were provided. Subjects who did not have sufficient measurements to establish efficacy were considered non-responders (i.e., non-responder imputation [NRI]).

In the analyses of efficacy endpoints, stratification factors were included as covariates in the analysis model. If there were discrepancies in stratification factor values between the IWRS and the clinical database, the values recorded in the clinical database were to be used for analyses.

For continuous endpoints, change from baseline in e.g. HAQ-DI and mTSS were analysed using a mixed-effects model for repeated measures (MMRM) with baseline value, stratification factors, treatment, visit, and treatment by visit interaction, included as fixed effects and subject being the random effect. The hypothesis testing for secondary analyses commenced after the primary analysis had reached statistical significance and was tested according to the hierarchical testing principle using a 2-sided 0.05 level.

Results

Participant flow

Out of the 2582 patients screened, 1759 patients were randomized. Four subjects (2 in the filgotinib 200 mg arm and 2 in the placebo arm) were randomized but not dosed. At cut-off date (of the initial submission), 304 (17.3%) had prematurely discontinued study drug. A similar proportion of subjects in the three active treatment arms had prematurely discontinued study drug. Up to the cut-off date (of the initial submission), 11.5% had prematurely discontinued study.

Baseline data

Most subjects were female (81.8%) and the mean (SD) age was 53 (12.7) years (safety analysis set). Presence of anti-CCP was 80.0% in Filgotinib 200 mg, 79.4% in Filgotinib 100 mg, 77.8% in Adalimumab and 79.6% in the Placebo group. Mean (SD) DAS28 CRP was 5.8 (0.88) in Filgotinib 200 mg, 5.7 (0.95) in Filgotinib 100 mg, 5.7 (0.88) in the Adalimumab and 5.7 (0.91) in the Placebo group. The proportion with Erosion score>0 was 84.0% in Filgotinib 200 mg, 85.6% in Filgotinib 100 mg, 85.2% in Adalimumab and 85.1% in the placebo group.

Numbers analysed

The Full Analysis Set (FAS) included all randomised subjects (n=1759) who received at least 1 dose of study drug (n=1755); this was the primary analysis set for efficacy analyses. The Per-Protocol Analysis Set (n=1649) was the secondary analysis set for efficacy analyses on primary and key secondary endpoints.

For analyses based on FAS, subjects were grouped according to the treatment to which they were randomised.

Outcomes and estimation

In FINCH 1, all superiority or noninferiority tests of filgotinib versus comparator in the hierarchical testing demonstrated a statistically significant superiority or noninferiority of filgotinib over the comparator ($p < 0.001$), with the exception of the final noninferiority test of the percentages of subjects who achieved DAS28(CRP) $\leq$ 3.2 at Week 12 (filgotinib 100 mg vs adalimumab; $p = 0.054$), see *Table 13*.

Table 13: GS-US-417-0301: SAP 2, Hierarchical Testing of the Superiority of Filgotinib versus Placebo or Noninferiority versus Adalimumab

Endpoint[a]	Time Point	Filgotinib Dose[b]	Comparator	P-value
ACR20[c]	Week 12	200 mg	placebo	p < 0.001
DAS28(CRP) ≤ 3.2	Week 12	200 mg	placebo	p < 0.001
HAQ-DI	Week 12	200 mg	placebo	p < 0.001
DAS28(CRP) < 2.6	Week 24	200 mg	placebo	p < 0.001
ACR20	Week 12	100 mg	placebo	p < 0.001
DAS28(CRP) ≤ 3.2	Week 12	100 mg	placebo	p < 0.001
HAQ-DI	Week 12	100 mg	placebo	p < 0.001
DAS28(CRP) < 2.6	Week 24	100 mg	placebo	p < 0.001
mTSS	Week 24	200 mg	placebo	p < 0.001
mTSS	Week 24	100 mg	placebo	p < 0.001
DAS28(CRP) ≤ 3.2[b]	Week 12	200 mg	adalimumab	p < 0.001
DAS28(CRP) ≤ 3.2[b]	Week 12	100 mg	adalimumab	p = 0.054

SAP 2 is based on the analysis hierarchy specified in the protocol.
a ACR20, DAS28(CRP) ≤ 3.2, and DAS28(CRP) < 2.6 were binary endpoints; HAQ-DI, SF-36 PCS, FACIT-Fatigue, and mTSS were assessed using change from baseline.
b Noninferiority
c Primary endpoint

For the primary endpoint, ACR 20 at week 12, the proportion of responders were 76.6% in the Filgotinib 200 mgx1 (+MTX) group, 69.8% in the Filgotinib 100 mgx1(+MTX) group, 70.8% in the Adalimumab (+ MTX) group and 49.9% in the placebo (+ MTX) group ($p<0.001$ for both superiority comparisons between the Filgotinib groups and the placebo group).

For the key secondary endpoint LDA (defined as DAS28 (CRP)≤3.2) at week 12, the proportion of responders were 49.7% in the Filgotinib 200 mgx1(+MTX) group, 38.8% in the Filgotinib 100 mgx1(+MTX) group, 43.4% in the adalimumab (+ MTX) group and 23.4% in the placebo (+ MTX) group ($p<0.001$ for both superiority comparisons between the Filgotinib groups and the placebo group and for the non-inferiority comparison of Filgotinib 200 mg group vs the adalimumab group). Non-inferiority of Filgotinib 200 mg vs adalimumab for DAS28(CRP) <= 3.2 at Week 12 was confirmed also in the Per-Protocol analysis.

For the key secondary endpoint, change from baseline in the HAQ-DI score at Week 12, the mean (SD) was -0.69 (0.613) in Filgotinib 200 mg(+ MTX), -0.56 (0.564) in Filgotinib 100mg(+ MTX), -0.61 (0.559) in Adalimumab (+ MTX) and -0.42 (0.544) in the Placebo (+ MTX) group ($p<0.001$ for both superiority comparisons between the Filgotinib groups and the placebo group).

For the key secondary endpoint, the proportion of subjects who achieve Remission (defined as DAS28 (CRP)<2.6) at Week 24, the proportion of responders were 48.4% in the Filgotinib 200 mg (+ MTX) group, 35.2% in the Filgotinib 100 mg (+ MTX) group, 35.7% in the Adalimumab (+ MTX) group and 16.2% in the placebo (+ MTX) group ($p<0.001$ for both superiority comparisons between the Filgotinib groups and the placebo group).

For the key secondary endpoint, change from Baseline in mTSS at Week 24, the mean (SD) was 0.13 (0.937) in the Filgotinib 200 mg (+ MTX) group, 0.17 (0.905) in the Filgotinib 100 mg (+ MTX) group, 0.16 (0.948) in the Adalimumab group (+ MTX) and 0.38 (1.408) in the Placebo (+ MTX) group ($p<0.001$ for both superiority comparisons between the Filgotinib groups and the placebo group).

Numerically better outcomes were reported for both doses of Filgotinib compared to placebo for the PROs Change from Baseline in SF-36 PCS score at Week 12 and Change from Baseline in FACIT-Fatigue score at week 12 as well as for the CRP-independent outcome CDAI.

Regarding long-time efficacy, at week 24, the number of ACR 20 responders in absolute numbers increased vs week 12 in all groups but in particular in the placebo group. This was true also for the numbers of subjects that achieved DAS28 (CRP) <2.6 and DAS28 (CRP) <= 3.2 at week 12 vs week 24.

In response to the Day 120 LoQ, the final CSR with week 52-data was provided. The absolute number of ACR 20 responders in the Filgotinib 200 mg-group increased from week 12 to week 24 and did not decrease from week 24 to week 52. For the Filgotinib 100 mg group and the adalimumab group, a similar pattern was seen. The ACR 20 response increased among placebo subjects that subsequently received Filgotinib. For LDA, the absolute number of responders increased in all treatment groups through week 12-24-52. Also with regards to remission, the absolute number of subjects increased from week 24 to week 52 in all three active treatment groups. Finally, data supporting maintenance of effect in HAQ-DI and ACR50 and ACR 70 as well as week 52 radiological data, were also presented.

Ancillary analyses

Compared to placebo, a beneficial effect of Filgotinib was seen across the analysed subgroups with regard to achievement of the primary endpoint, although there were some differences regarding for example the efficacy in seropositive vs seronegative, BMI, race and geographic region.

FINCH 2 (GS-US-417-0302): A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 24 Weeks in Combination with Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug(s) (csDMARDs) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Biologic DMARD(s) Treatment

Methods

Study Participants and Treatments

FINCH 2 is a placebo-controlled, csDMARD-add on study that included a third line population (failed or intolerant to at least 1 bDMARD) that were randomized to either Filgotinib 100 mgx1, Filgotinib 200 mgx1 or placebo. There was a rescue-possibility to SOC at week 14 (in case ≥20% improvement in SJC and TJC had not been achieved). Concomitant csDMARDs included MTX, hydroxychloroquine, sulfasalazine and leflunomide. Exclusion criteria include prior treatment B-cell depleting agent within 6 months prior to Day 1 and use of non-cell depleting bDMARDs within 4 weeks prior to Day 1.

Upon completion of the 24-week dosing period, all subjects, regardless of response, who had not discontinued the study due to toxicity, were given the option to screen for enrolment into the separate LTE study; FINCH 4.

Objectives

Primary objective

To evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving an ACR20 response at Week 12 (superiority hypothesis).

Outcomes/endpoints

Primary endpoint was the proportion of subjects who achieved an ACR20 response at Week 12.

Key secondary efficacy endpoints were (according to the protocol and SAP 2): The proportion of subjects who achieve DAS28 (CRP) ≤3.2 (=LDA) at Week 12 and Change from baseline in the HAQ-DI score at Week 12.

These primary and key secondary endpoints were also measured at time points up to Week 24 and over time from Day 1 through Week 24. Additional endpoints included measurements of DAS28(CRP) < 2.6, the SF-36 Physical Component Summary (PCS) score, the FACIT-Fatigue score and CDAI.

Statistical methods, randomisation and blinding

Initially, approximately 423 subjects, 141 per treatment arm, were to be randomised to filgotinib 200 mg, filgotinib 100 mg, or placebo. Analogous study GS-US-417-0301 (FINCH1), the sample size was driven by a key secondary endpoint; change from baseline in HAQ-DI at Week 12, implying a power >90% for the primary endpoint. Randomisation was performed using an Interactive Web Response System (IWRS) stratified by geographic region (group A to E), prior exposure to number of bDMARDs (< 3 or ≥3 bDMARDs) and seropositivity (presence of rheumatoid factor (RF) or anti-CCP (cyclic citrullinated peptide) antibody (Ab) at screening). Masking was achieved using double-dummy technique and seems to have been appropriate.

Geographic region comprised 5 strata with the following countries included:

- Group A: Australia, Belgium, France, Germany, Israel, Italy, Netherlands, South Korea, Spain, Switzerland, United Kingdom, and USA;
- Group B: Hungary, Czech Republic and Poland;
- Group C: Argentina, Puerto Rico and Mexico;
- Group D: China;
- Group E: Japan

The statistical analysis approach shared a number of features with FINCH1. The statistical methods used were described in two SAPs; the analysis plan version 1.0 (EMA) was dated 23 August 2018. The finalisation of the database and treatment unblinding was on the 24 August 2018. Two efficacy estimands, composite estimand and treatment-policy estimand were defined for the primary and key secondary efficacy endpoints, respectively and efficacy analysis were conducted using two datasets; On-treatment data and All available data (including data collected under standard of care). Analyses using both approaches were planned and have been performed for the primary as well as key secondary endpoints.

For binary endpoints including the primary endpoint, statistical inference was based on the p-value from a logistic regression analysis with treatment groups and stratification factors in the model. Subjects who did not have sufficient measurements to establish efficacy at Week 12 were considered non-responders. In the primary analysis of the primary endpoint, this included subjects who had discontinued randomised treatment early or needed SOC due to inadequate treatment response. For the difference between treatment arms, the non-stratified ACR20 response rate difference along with corresponding 95% CI were provided. Continuous endpoints were analysed using a mixed-effects model for repeated measures (MMRM) with baseline value, stratification factors, treatment, visit, and treatment by visit interaction, included as fixed effects and subject being the random effect.

In the analyses of the primary and key secondary endpoints, missing data was either handled using a non-responder imputation (categorical/response rates) or implicitly through the use of MMRM.

The confirmatory hierarchical testing strategy comprised the primary endpoint and two key secondary endpoints; all three hypotheses for the comparison of the higher dose (200 mg) versus placebo were to be tested and found positive before the same hypotheses, including the analysis of the primary endpoint, was to be formally tested for the lower dose vs placebo.

Results

Participant flow

Out of the 688 subjects screened, 449 subjects were randomised, and 448 subjects were both randomised and treated. Out of these, 108 subjects (24.1%) prematurely discontinued study drug (14.3% in the Filgotinib 200 mg group, 22.9% in the Filgotinib 100 mg group and 35.1% in the placebo group). Of the 52 subjects that discontinued study drug in the placebo group, 32 subjects discontinued due to lack of efficacy. Overall, 15.0% discontinued the study prematurely (8.2% in the Filgotinib 200 mg group, 15.0% in the Filgotinib 100 mg group and 21.6% in the placebo group).

Baseline data

Most subjects were female (80.4%) and the mean (SD) age was 56 (12.2) years.

Presence of anti-CCP was 67.3% in Filgotinib 200 mg, 73.9% in Filgotinib 100 mg and 70.9% in placebo group. Mean (SD) DAS28 CRP was 5.9 (1.03) in Filgotinib 200 mg, 5.9 (0.98) in Filgotinib 100 mg and 5.9 (0.86) in the placebo group.

Number of prior bDMARD exposure ≥ 3 bDMARDs was 25.2% in the Filgotinib 200 mg, 22.2% in Filgotinib 100 mg and 23.0% in the placebo group. Concurrent Methotrexate Use on First Dosing Date was 84.4% in Filgotinib 200 mg, 83.0% in Filgotinib 100 mg and 78.4% in the placebo group.

Numbers analysed

The FAS included all subjects who were randomised (n=449) and received at least 1 dose of study drugs (n=448) and was the primary analysis set for efficacy analyses. The Per-Protocol (PP) Analysis Set (n=397) was the secondary analysis set for efficacy analyses.

For analyses based on the FAS, subjects were grouped according to the treatment to which they were randomised.

Outcomes and estimation

In FINCH 2, Filgotinib 200 mgx1 (+csMARD) or 100 mgx1 (+ csMARD) showed superiority over placebo (+csMARD) for the primary endpoint and all key secondary endpoints, see *Table 14*.

Table 14: GS-US-417-0302: SAP 2–Hierarchical Testing of the Superiority of Filgotinib Versus Placebo (after the primary endpoint reached statistical signficance)

Endpoint[a]	Time Point	Filgotinib Dose	P-value
DAS28(CRP) ≤ 3.2	Week 12	200 mg	p < 0.001
HAQ-DI	Week 12	200 mg	p < 0.001
ACR20	Week 12	100 mg	p < 0.001
DAS28(CRP) ≤ 3.2	Week 12	100 mg	p < 0.001
HAQ-DI	Week 12	100 mg	p < 0.001

a ACR20 and DAS28(CRP) ≤ 3.2 were binary endpoints; HAQ-DI was assessed using change from baseline.

The proportion that attained the primary endpoint, ACR 20 at week 12, was 66.0% in the Filgotinib 200 mgx1 (+csDMARD) group, 57.5% in the Filgotinib 100 mg (+csDMARD) group and 31.1% in the placebo (+csDMARD) group (p<0.001 for both the comparison between the Filgotinib groups and placebo).

For the key secondary endpoint, proportion of subjects who achieved LDA (defined as DAS28 [CRP] ≤ 3.2) at Week 12, it was 40.8% in the Filgotinib 200 mgx1 (+csDMARD) group, 37.3% in the Filgotinib 100 mgx1 (+csDMARD) group and 15.5% in the placebo (+csDMARD) group (p < 0.001 for both comparisons with placebo).

For the key secondary endpoint change from baseline in the HAQ-DI score at Week 12, the mean (SD) was -0.55 (0.590) in the Filgotinib 200 mg (+csDMARD) group, -0.48 (0.602) in the Filgotinib 100 mg (+csDMARD) group and -0.23 (0.547) in the placebo (+csDMARD) group.

Numerically better response was seen for both tested doses of Filgotinib vs placebo with regards to SF-36 PCS and FACIT-fatigue score at Week 12. Differences vs placebo was also seen for both doses with regards to the CRP-independent measure CDAI.

Numerically better improvements were seen Filgotinib vs placebo for primary and key secondary endpoints from week 2-4 through week 24. In addition, data supporting an effect on ACR 50 and 70 week, 12 and week 24, were presented.

Ancillary analyses

Compared to placebo, a beneficial effect of Filgotinib was seen across the investigated subgroups with regards to achievement of the primary endpoint although there were some differences regarding for example the efficacy in seropositive vs seronegative, BMI, race and geographic region**.**

FINCH 3 (GS-US-417-0303): A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 Weeks Alone and in Combination with Methotrexate (MTX) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are Naïve to MTX Therapy

Methods

Study Participants and Treatments

FINCH 3 is an active-controlled study that included a first line population (limited or no prior treatment with MTX) with at least one poor prognostic factor that were randomized to either Filgotinib 100 mgx1+MTX, Filgotinib 200 mgx1+MTX, Filgotinib 200 mgx1 monotherapy or MTX monotherapy with a rescue-possibilities to SOC from week 24 (if a 20% improvement in both SJC and TJC was not reached). Antimalarials are included among the permitted concomitant medications.

After having completed this study, subject could continue in the LTE FINCH 4.

Objectives

Primary objective

To evaluate the effects of filgotinib in combination with MTX versus MTX monotherapy for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving ACR20 at Week 24 (superiority hypothesis).

Outcomes/endpoints

The primary endpoint was the proportion of subjects who achieved an ACR20 response at Week 24.

The key secondary efficacy endpoints in the protocol and in SAP 2 were: Change from baseline in the HAQ-DI score at Week 24, The proportion of subjects who achieved DAS28(CRP) < 2.6 at Week 24 (=remission) and Change from baseline in the mTSS at Week 24.

Statistical methods, randomisation and blinding

The planned total sample size was 1200; 400 subjects for filgotinib 200 mg in combination with MTX group, 200 subjects for filgotinib 100 mg in combination with MTX group, 200 subjects for filgotinib 200 mg alone group and 400 subjects for MTX alone group. The sample size was driven by the expected difference of filgotinib 200 mg + MTX versus MTX in change from baseline in mTSS at Week 24. The power for comparisons on the primary endpoint was >90%.

Eligible subjects were randomised via an IWRS in a 2:1:1:2 ratio to filgotinib 200 mg + MTX, filgotinib 100 mg + MTX, filgotinib 200 mg alone, or MTX alone, for up to 52 weeks. Randomisation was stratified by geographic region (Group A to E) and presence of rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibody (anti-CCP Ab) at screening.

The regions included the following countries:

- Group A: United States of America, Spain, Germany, Republic of Korea, Canada, Belgium, South Africa, Australia, New Zealand, United Kingdom, Italy, Ireland and Israel
- Group B: India, Poland, Ukraine, Bulgaria, Russian Federation, Czech Republic, Hungary, Serbia, Romania and Slovakia
- Group C: Mexico, Argentina and Chile
- Group D: Taiwan, Thailand, Malaysia, Hong Kong
- Group E: Japan

Masking of treatment was achieved by the use of placebo to match filgotinib tablets and placebo to match MTX capsules.

The SAP Version 1.0 (EMA) was dated 31 January 2019. A planned Week 24 analysis was conducted after all subjects had either completed the Week 24 visit or had prematurely discontinued from the study. The date for the database finalisation and treatment unblinding for the current interim report was 17 January 2019 and 01 February 2019, respectively. The final analysis of the data will be performed after all subjects have completed the study. The primary analyses consisted of a superiority test of filgotinib 200 mg + MTX

compared with MTX monotherapy based on the primary endpoint. Superiority was tested at the 2-sided 0.05-level. A logistic regression analysis with treatment groups and stratification factors in the model was used. Subjects who did not have sufficient measurements to establish efficacy at Week 24 were considered non-responders. If the superiority of filgotinib 200 mg + MTX over MTX monotherapy was established, hypothesis testing for the secondary analyses was initiated. The superiority of filgotinib 200 mg + MTX or filgotinib 100 mg + MTX over MTX monotherapy was tested according to the hierarchical testing principle at the 2-sided 0.05-level. The change from baseline in HAQ-DI score, mTSS, SF-36 PCS, and FACIT-Fatigue score were analysed using a mixed-effects model for repeated measures (MMRM). In addition to the FAS, analyses were based on the Per Protocol (PP) Analysis Set, additional sensitivity analyses included observed case (OC) and last observation carried forward (LOCF) (for binary endpoints), multiple imputation (MI), and tipping point analyses. Analyses of the primary and key secondary efficacy endpoints, as well as other secondary efficacy endpoints were repeated using all available data, including assessments collected under standard of care.

Results

Participant flow

Of the 1855 subjects screened, 1252 were randomized and 1249 were both randomized and dosed. Up to Week 24, 1130 of these 1249 subjects (90.5%) remained on study: 376 subjects (90.4%) in the filgotinib 200 mg + MTX group, 193 subjects (93.2%) in the filgotinib 100 mg + MTX group, 188 subjects (89.5%) in the filgotinib 200 mg monotherapy group, and 373 subjects (89.7%) in the MTX monotherapy group.

Up to Week 24, 119 subjects (9.5%) of the 1249 subjects prematurely discontinued study drug and these were distributed as follows: filgotinib 200 mg + MTX: 40 subjects (9.6%); filgotinib 100 mg + MTX: 14 subjects (6.8%); filgotinib 200 mg monotherapy: 22 subjects (10.5%); and MTX monotherapy: 43 subjects (10.3%).

Baseline data

Most subjects were female (76.9%) and the mean (SD) age was 53 (13.6) years.

In total, 9.4% had concurrent antimalarials use; 8.4% in the Filgotinib +MTX group, 11.6% in the Filgotinib 100 mg + MTX group, 8.6% in the Filgotinib monotherapy group and 9.9% in the MTX monotherapy group. Overall, 77.4% were DMARD naïve; ranging from 76.9% in the Filgotinib 200 mg + MTX group to 78.1% in the Filgotinib 200 mg monotherapy group.

Presence of aCCP was 69.0% in the Filgotinib 200 mg + MTX group, 69.1% in the Filgotinib 100 mg +MTX group, 63.3% in the Filgotinib 200 mg monotherapy group and 70.2% in the MTX monotherapy group. Mean (SD) DAS28 CRP was 5.7 (0.99) in the Filgotinib 200 mg + MTX group, 5.7 (1.04) in the Filgotinib 100 mg + MTX group, 5.8 (0.94) in the Filgotinib 200 mg monotherapy group and 5.7 (1.00) in the MTX monotherapy group. The proportion with Erosion Score > 0 was 94.2% in the Filgotinib 200 mg+MTX group, 95.7% in the Filgotinib 100 mg +MTX group, 94.8% in the Filgotinib 200 mg monotherapy group and 92.5% in the MTX monotherapy group.

Numbers analysed

The primary efficacy analysis used the FAS, which included all subjects who were randomized (n=1252) and received at least 1 dose of study drug (n=1249). The primary and key secondary endpoints were also evaluated based on the PP Analysis Set (n=1160), the secondary analysis set for efficacy analysis.

For analyses based on FAS, subjects were grouped according to the treatment to which they were randomized.

Outcomes and estimation

FINCH 3 met its primary endpoint demonstrating the superiority of filgotinib 200 mg + MTX over MTX monotherapy on the ACR20 response rate at Week 24. Moreover, Filgotinib 200 mg + MTX and Filgotinib 100 mg + MTX demonstrated superiority over MTX monotherapy for ACR20, HAQ-DI, and DAS28(CRP) < 2.6 at Week 24. The formal sequential testing according to SAP 2 was stopped at step 7 and only nominal significance was reported for the remaining hypotheses, see table below.

Table 15: GS-US-417-0303: SAP 2, Hierarchical Testing of the Superiority of Filgotinib versus MTX Monotherapy at Week 24 (Full Analysis Set)

Endpoint[a]	Filgotinib Dose[b]	P-Value
ACR20[c]	200 mg + MTX	< 0.001
HAQ-DI	200 mg + MTX	< 0.001
DAS28(CRP) < 2.6	200 mg + MTX	< 0.001
ACR20	100 mg + MTX	0.017
HAQ-DI	100 mg + MTX	0.009
DAS28(CRP) < 2.6	100 mg + MTX	< 0.001
ACR20	200 mg monotherapy	0.058
HAQ-DI	200 mg monotherapy	0.032[d]
DAS28(CRP) < 2.6	200 mg monotherapy	< 0.001[d]
mTSS	200 mg + MTX	0.061[d]
mTSS	100 mg + MTX	0.14[d]
mTSS	200 mg monotherapy	0.006[d]

a ACR20 and DAS28(CRP) < 2.6 were binary endpoints; HAQ-DI and mTSS were assessed using change from baseline
b Superiority of filgotinib dose versus MTX monotherapy
c Primary analysis endpoint
d Nominal p-values are provided for endpoints and doses that were not tested in the hierarchical testing procedure either due to failure of a prior endpoint or for those that were not included in the testing procedures. The nominal p-values are used to guide interpretation of the efficacy results, without the intention to declare statistical significance.

For the primary endpoint, ACR 20 response at week 24, this was reached by 81.0% in the Filgotinib 200 mgx1+MTX group, 80.2% in the Filgotinib 100 mg x1+MTX group, 78.1% in the Filgotinib 200 mg monotherapy group and 71.4% in the MTX monotherapy group (p<0.05 for the two comparisons between Filgotinib combination therapy vs MTX).

For the key secondary endpoint proportion with DAS28(CRP) < 2.6 i.e. remission at Week 24, this was achieved by 54.1% in the Filgotinib 200 mg 1x1 + MTX group, 42.5%, in the Filgotinib 100 mg 1x1+MTX, 42.4% in the Filgotinib 200 mg monotherapy group and 29.1% in the MTX monotherapy group (p < 0.001 for the comparisons with the two Filgotinib combination groups and MTX monotherapy group respectively).

For the key secondary endpoint, change from baseline in the HAQ-DI score at Week 24, the mean (SD) was -0.94 (0.721) in the Filgotinib 200 mg + MTX group, -0.90 (0.675) in the Filgotinib 100 mg +MTX group, -0.89 (0.631) in the Filgotinib 200 mg monotherapy group and -0.79 (0.634) in the MTX monotherapy group (p<0.001 for the comparison between Filgotinib 200 mg + MTX and MTX monotherapy, p = 0.009 for the comparison between Filgotinib 100 mg + MTX vs MTX monotherapy)

For the key secondary endpoint change from baseline in the mTSS at Week 24, the mean (SD) was 0.20 (1.682) in the Filgotinib 200 mg group, 0.22 (1.530) in the Filgotinib 100 mg group, -0.04 (1.710) in the Filgotinib 200 mg monotherapy group and 0.52 (2.892) in the MTX monotherapy group.

Change from Baseline in the PROs SF-36 PCS Score and Change from Baseline in FACIT-Fatigue Score at Week 24 was numerically greater in all Filgotinib arms compared to the MTX monotherapy arm. Also, mean improvement from baseline to week 24 in the CRP-independent measure CDAI was numerically higher for each filgotinib group versus MTX monotherapy.

Numerically greater ACR20 response rates versus MTX monotherapy were seen from Week 2 for the Filgotinib groups and through Week 24. This was observed also for the proportion of subjects in remission (DAS28 CRP<2.6).

In response to the Day 120 LoQ, the final CSR with week 52-data was provided. In all four treatment groups there was a slight decrease in the absolute number of ACR 20 responders from week 24 to week 52. In the Filgotinib + MTX arms, the absolute number in remission were essentially the same week 24 and week 52 while it increased somewhat from week 24 to week 52 in the Filgotinib mono-arm and the MTX arm. Data supporting an effect of filgotinib on ACR 50, ACR 70 and HAQ-DI up to 1 year (52 weeks), as well as week 52 radiological data, were also presented.

Ancillary analysis

Compared to MTX monotherapy, a beneficial effect of Filgotinib measured as ACR 20 was present across investigated subgroups although there were some differences with regards to for example seropositivity, BMI, region, race and age.

2.5.2.1. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16: Summary of efficacy for FINCH 1

Title: FINCH 1 (GS-US-417-0301): A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 weeks in Combination with Methotrexate to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate		
Study identifier	IND No.: 115510 EudraCT No.: 2016-000568-41 ClinicalTrials.gov Identifier: NCT02889796	
Design	Randomized, Double-blind, Placebo- and Active-controlled parallel, multi-centre, **MTX add-on, Second line**	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks not applicable at completion, option to enrol in LTE study GS-US-417-0304 (FINCH 4)
Hypothesis	Superiority	
Treatments groups	Filgotinib 200 mg	52 weeks, number randomized= 477
	Filgotinib 100 mg	52 weeks, number randomized=480

	Adalimumab 40 mg		52 weeks, number randomized=325
	Placebo		24 weeks, number randomized=477
Endpoints and definitions	Primary endpoint	ACR20 response at Week 12	
	Most relevant Key Secondary Endpoint	LDA at week 12	DAS28 (CRP)⩽3.2 at Week 12
Database lock	Database finalization for interim 05 Feb 2019, treatment unblinding for interim 07 Feb 2019		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	The Full Analysis Set (FAS) =all randomized subjects who received at least 1 dose of study drug was the primary analysis set for efficacy analyses				
Descriptive statistics and estimate variability	Treatment group	Filgotinib 200 mg	Filgotinib 100 mg	Adalimumab 40 mg	Placebo
	Number FAS	475	480	325	475
	ACR 20 week 12	76.6%	69.8%	70.8%	49.9%
	95% CI	72.7%; 80.5%	65.6%; 74.0%	65.7%;75.9%	45.3%;54.5%
	LDA week12	49.7%	38.8%	43.4%	23.4%
	95% CI	45.1%;54.3%	34.3%; 43.2%	37.8%;48.9%	19.5%;27.3%

Effect estimate per comparison	Primary endpoint: ACR20 week 12	Comparison groups	Filgotinib 200 mg vs placebo
		Difference in Response rates	26.7%
		95% CI of Difference in Response Rates	20.6%; 32.8%
		P-value	<0.001
	Primary endpoint:	Comparison groups	Filgotinib 100 mg vs placebo

	ACR 20 week 12	Difference in ACR 20 response rates	19.9%
		95% CI of Difference in Response rates	13.6%; 26.2%
		P-value	<0.001
	LDA at week 12	Comparison groups	Filgotinib 200 mg vs placebo
		Difference in Response rates	26.3%
		95% CI of Difference in Response Rates	20.2%; 32.4%
		P-value	<0.001
	LDA at week 12	Comparison groups	Filgotinib 100 mg vs placebo
		Difference in Response rates	15.4%
		95% CI of Difference in Response Rates	9.4%;21.4%
		P-value	<0.001
Notes	NA		

Table 17: Summary of efficacy for FINCH 2

Title: FINCH 2 (GS-US-417-0302): A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 24 Weeks in Combination with Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug(s) (csDMARDs) to Subjects with Moderately to Severely Active Rheumatoid Arthritis		
Study identifier	IND No.: 115510 EudraCT No.: 2016-000569-21 ClinicalTrials.gov Identifier: NCT02873936	
Design	Randomized, double-blind, parallel, multicentre, **csDMARD add-on, third line**	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks not applicable at completion, option to enrol in LTE study GS-US-417-0304 (FINCH 4)
Hypothesis	Superiority	
Treatments groups	Filgotinib 200 mg	24 weeks, number randomized=148

	Filgotinib 100 mg		24 weeks, number randomized=153
	Placebo		24 weeks, number randomized=148
Endpoints and definitions	Primary endpoint	ACR 20 at week 12	
	Most relevant key secondary endpoint: LDA	LDA at week 12	DAS28 (CRP)≤3.2
Database lock	24 August 2018 database Finalization and Treatment Unblinding		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The Full Analysis Set (FAS) =all randomized subjects who received at least 1 dose of study drug was the primary analysis set for efficacy analyses			
Descriptive statistics and estimate variability	Treatment group	Filgotinib 200 mg	Filgotinib 100 mg	Placebo
	Number FAS	147	153	148
	ACR 20 week 12	66.0%	57.5%	31.1%
	95% CI	58.0%; 74.0%	49.4%; 65.7%	23.3%; 38.9%
	LDA week12	40.8%	37.3%	15.5%
	95% CI	32.5%; 49.1%	29.3%; 45.2%	9.4%; 21.7%

Effect estimate per comparison	Primary endpoint: ACR20 week 12	Comparison groups	Filgotinib 200 mg vs Placebo
		Difference in Response Rates	34.9%
		95% CI of Difference in Response Rates	23.5%; 46.3%
		P-value	<0.001
	Primary endpoint:	Comparison groups	Filgotinib 100 mg vs Placebo

	ACR20 week 12	Difference in Response Rates	26.4%
		95% CI of Difference in Response Rates	15.0%; 37.9%
		P-value	<0.001
	LDA at week 12	Comparison groups	Filgotinib 200 mg vs Placebo
		Difference in Response Rates	25.3%
		95% CI of Difference in Response Rates	14.7%; 35.8%
		P-value	< 0.001
	LDA at week 12	Comparison groups	Filgotinib 100 mg vs placebo
		Difference in Response Rates	21.7%
		95% CI of Difference in Response Rates	11.4%, 32.0%
		P-value	< 0.001
Notes	Not applicable.		

Table 18: Summary of efficacy for FINCH 3

Title: 3.3.3. FINCH 3(GS-US-417-0303): A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 Weeks Alone and in Combination with Methotrexate (MTX) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are Naïve to MTX Therapy		
Study identifier	IND No.: 115510 EudraCT No.: 2016-000570-37 ClinicalTrials.gov Identifier: NCT02886728	
Design	Randomized, double-blind, multi-centre, **first line** (MTX naïve)	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks not applicable possibility for continuing in LTE study
Hypothesis	Superiority	
Treatments groups	Filgotinib 200 mg + MTX	52 weeks, number randomized=417
	Filgotinib 100 mg + MTX	52 weeks, number randomized=207
	Filgotinib 200 mg monotherapy	52 weeks, number randomized=210
	MTX monotherapy	52 weeks, number randomized=418

Endpoints and definitions	Primary endpoint	ACR 20 week 24	
	Most relevant Key Secondary endpoint	Remission week 24	DAS28(CRP) < 2.6 at Week 24.
Database lock	17 Jan 2019 database finalization for interim CSR, 01 Feb 2019 treatment unblinding		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	The Full Analysis Set (FAS) =all randomized subjects who received at least 1 dose of study drug was the primary analysis set for efficacy analyses				
Descriptive statistics and estimate variability	Treatment group	Filgotinib 200 mg + MTX	Filgotinib 100 mg + MTX	Filgotinib 200 mg monotherapy	MTX monotherapy
	Number FAS	416	207	210	416
	ACR 20 week 24	81.0%	80.2%	78.1%	71.4%
	95% CI	77.1%;84.9%	74.5%;85.9%	72.3%;83.9 %	66.9%;75.9%
	Remission week 24	54.1%	42.5%	42.4%	29.1%
	95% CI	49.2%; 59.0%	35.5%, 49.5%	35.5%; 49.3%	24.6%; 33.6%

Effect estimate per comparison	Primary endpoint: ACR 20 week 24	Comparison groups	Filgotinib 200 mg +MTX vs MTX monotherapy
		Difference in Response rates	9.6%
		95% CI of Difference in Response Rates	3.6%; 15.6%
		p-value	<0.001
	Primary Endpoint: ACR 20 week 24	Comparison groups	Filgotinib 100 mg + MTX vs monotherapy
		Difference in Response rates	8.8%

		95% CI of Difference in Response Rates	1.5%; 16.1%
		P-value	0.017
	Primary Endpoint: ACR 20 week 24	Comparison groups	Filgotinib 200 mg monotherapy vs MTX monotherapy
		Difference in Response rates	6.7%
		95% CI of Difference in Response Rates	-0.7%; 14.1%
		P-value	0.058
Effect estimate per comparison	Most relevant key secondary endpoint: Remission at week 24	Comparison groups	Filgotinib 200 mg +MTX vs MTX monotherapy
		Difference in Response rates	25.0%
		95% CI of Difference in Response Rates	18.3%, 31.7%
		p-value	<0.001
	Most relevant key secondary endpoint: Remission at week 24	Comparison groups	Filgotinib 100 mg + MTX vs monotherapy
		Difference in Response rates	13.4%
		95% CI of Difference in Response Rates	5.0%, 21.8%
		P-value	<0.001
	Most relevant key secondary endpoint: Remission at week 24	Comparison groups	Filgotinib 200 mg monotherapy vs MTX monotherapy
		Difference in Response rates	13.3%
		95% CI of Difference in Response Rates	5.0%, 21.6%
		P-value	<0.001 (nominal)

Analysis performed across trials: pooled analyses and meta-analysis

No meta-analysis and pooled analysis relevant with clear importance for the efficacy assessment were presented.

Clinical studies in special populations

There were no dedicated clinical studies focusing on efficacy in children, the elderly or patients with renal/hepatic impairment within the target indication (RA).

The Applicant performed 3 phase 1 studies with filgotinib 100 mg in subjects: one with impaired hepatic function, one with renal impairment and one in elderly healthy subjects, please refer to Section 2.4.

The number of subjects per age group in the filgotinib development programme is presented in *Table 19*.

Table 19: Number of Subjects per Age Group in Filgotinib RA Clinical Studies (Safety Analysis Set)

	Age < 65 years (Subjects Number/ Total Number)	Age 65-74 years (Older Subjects Number/ Total Number)	Age 75-84 years (Older Subjects Number/ Total Number)	Age 85+ years (Older Subjects Number/ Total Number)
Controlled RA Trials: Total (N = 4693)	3818/4693 (81.4%)	719/4693 (15.3%)	153/4693 (3.3%)	3/4693 (< 0.1%)
Controlled RA Trials: Phase 1 Studies[a] (N = 152)	152/152 (100.0%)	0/152	0/152	0/152
Controlled RA Trials: Phase 2 Studies[b] (N = 1089)	912/1089 (83.7%)	152/1089 (14.0%)	25/1089 (2.3%)	0/1089
Controlled RA Trials: Phase 3 Studies[c] (N = 3452)	2754/3452 (79.8%)	567/3452 (16.4%)	128/3452 (3.7%)	3/3452 (< 0.1%)
Noncontrolled RA Trials: Total (N = 3162)	2517/3162 (79.6%)	513/3162 (16.2%)	130/3162 (4.1%)	2/3162 (< 0.1%)
Noncontrolled RA Trials: Long-Term Extension Study (GLPG0634-CL-205) (N = 739)	619/739 (83.8%)	104/739 (14.1%)	16/739 (2.2%)	0/739
Noncontrolled RA Trials: Long-Term Extension Study (GS-US-417-0304) (N = 2423)	1898/2423 (78.3%)	409/2423 (16.9%)	114/2423 (4.7%)	2/2423 (< 0.1%)

a Controlled Phase 1 studies include GLPG0634-CL-101, GLPG0634-CL-102, GLPG0634-CL-110, and GS-US-417-3911.
b Controlled Phase 2 studies include GLPG0634-CL-201, GLPG0634-CL-202, GLPG0634-CL-203, GLPG0634-CL-204, GLPG0634-CL-227, and GS-US-379-1582. Study GLPG0634-CL-227 includes psoriatic arthritis, ankylosing spondylitis, and RA patients, and only RA patients are counted toward this table
c Controlled Phase 3 studies include GS-US-417-0301, GS-US-417-0302, and GS-US-417-0303.
Note that subjects included in the noncontrolled RA trials are counted twice; once in the parent study in which they were enrolled and then in the long-term extension study into which they rolled over.

Supportive studies

Not applicable.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Extent of the development program supporting clinical efficacy

The indication initially proposed by the Applicant encompassed: monotherapy and combination with MTX ≥ second line as well as monotherapy first line. In the approved indication, the first line indication has been omitted.

The efficacy data to support all parts of this proposed indication derives from:

- 5 Phase II studies in an MTX-IR population (GLPG0634-CL-201, GLPG0634-CL-202, GLPG0634-CL-203, GLPG0634-CL-204; DARWIN 1-2 and the long-term extension study GLPG0634-CL-205; DARWIN 3)
- 4 Phase III studies; in a MTX-IR population (Study GS-US-417-0301; FINCH 1), in a bDMARD-IR population (Study GS-US-417-0302; FINCH 2), in an MTX-naive population (Study GS-US-417-0303; FINCH 3), and one long-term extension study (Study GS-US-417-0304; FINCH 4).

The duration of FINCH 2 (bDMARD-IR population) was only 24 weeks while the other two-phase III studies were of 52 weeks duration. In the initial submission, only data up to 24 weeks were included (in 24 week-CSRs). In the response to the Day 120 LoQ, the final CSRs with week 52-data were provided. Long-term safety and efficacy data from FINCH 4 Study, that enrols subjects from the three Phase 3 studies, will be submitted by 2Q 2021.

Design and conduct of phase II studies; dose response studies

Two completed 4-week Phase 2a studies; GLPG0634-CL-201 and GLPG0634-CL-202, explored once or twice daily filgotinib doses up to a total daily dose of 200 mg or 300 mg on top of MTX, respectively. Doses above 200 mg daily were not pursued in Phase 2b because an exposure-response analysis was considered to have demonstrated that responses were at plateau with the 200-mg daily dose.

The phase 2b studies GLPG0634-CL-203; DARWIN 1 and GLPG0634-CL-204; DARWIN 2 included subjects exposed at 3 different daily doses of GLPG0634 i.e. filgotinib (i.e., 50, 100, and 200 mg daily) at 2 dose regimens (once and twice daily administration). Both studies; the first MTX-add on, the second monotherapy, were conducted in the MTX-IR population and were randomized, double-blind and placebo-controlled, with ACR 20 at week 12 being the primary endpoint and an NRI-approach. The design of the phase IIb dose-finding studies, including the selection of the primary endpoint, are generally considered acceptable.

Regarding DARWIN 2, it is noted that although this was considered as a monotherapy study, antimalarial DMARDs were included among the permitted medications. Given that a rather small proportion of subjects in the study were treated with antimalarials (approximately 10%), that this use was rather evenly distributed between the treatment groups and the known fairly modest treatment effect of antimalarials on RA, this condition is not expected to influence the overall conclusions to be drawn from this dose-finding study. However, as the Applicant indicated that the data from this study also supports the current monotherapy claim -and as this is actually the only study that provides data on monotherapy second line- the applicant was at Day 120 requested to re-analyse the data from this study (primary and key secondary endpoints with focus on endpoints reflecting low disease activity or remission) excluding subjects concomitantly treated with antimalarials (see outcome and discussion below).

Design and conduct of phase III studies; main studies

For the three Phase 3 RCT, the primary analysis consisted of a superiority test of filgotinib based on the ACR20 response rate (at week 12 in FINCH 1,2 and at week 24 in FINCH 3) with an NRI-approach.

FINCH 1 is a placebo and active-controlled MTX-add on study that included a second line population (active RA despite MTX-treatment) with poor prognostic factors that were randomized to either Filgotinib 100 mgx1, Filgotinib 200 mgx1, the TNF-inhibitor adalimumab or placebo, with a rescue-possibility (to SOC) at week 14. In addition to MTX, concomitant anti-malarial csDMARDs were allowed but no other csDMARDs. The patient population, overall design, timepoint for rescue and choice of comparator are in line with EMA RA guideline and previous SA. The choice of primary endpoint is not consistent with the new

EMA RA guideline from 2017 but was discussed at a central SA in 2016. In the SA, the CHMP commented that remission at month 6 or LDA at month 3, was the recommended endpoint and if the applicant would like to choose an ACR response measure as a primary endpoint and LDA as key secondary and testing both using a hierarchical strategy, the CHMP would consider the study positive if both endpoints were positive. Based on this advice, the outcome of the secondary endpoints reflecting LDA or remission was carefully considered in the evaluation of the outcome from FINCH 1.

FINCH 2 is a placebo-controlled, csDMARD-add on study that included a third line population (failed or intolerant to at least 1 bDMARD) that were randomized to either Filgotinib 100 mgx1, Filgotinib 200 mgx1 or placebo with a rescue-possibility (to SOC) at week 14. Concomitant csDMARDs included MTX, hydroxychloroquine, sulfasalazine and leflunomide and these are indeed considered as relevant csDMARDs to be tested in combination with the new drug. Overall, the study design is in line with relevant EMA guidelines regarding confirmatory RA trials and the timepoint for rescue is in line with the given central advice. However, the two following issues require some additional consideration.

First, in the SA April 2016, it was commented that the patient population to be studied in FINCH 2 was heterogeneous (as it included a mix of true third line patients and patients intolerant to bDMARDs that could be considered as second line population if the treatment duration was <3 months) and that across such mix, the most appropriate selection of primary endpoint could differ. It was stated that if the originally proposed heterogenous study population was to be maintained, the following requirements would at least have to be met: 1) the ACR 20 primary endpoint but would need to be supported by consistent results for LDA as key secondary endpoint and 2) the study would have be sufficiently large to support subgroup analyses across the heterogenous population so that consistency of effect for both AC20 and LDA could be verified. These remarks were considered when evaluating the main outcomes of the study (see below). It is noted that ACR 20 is the primary endpoint of FINCH 2 study but LDA, expressed as DAS28(CRP) $\leq$ 3.2, at week 12 is a ranked key secondary endpoint.

Second, in the relevant EMA RA guideline, the potential for residual response of prior bDMARD at the time of inclusion and sudden deterioration if the prior bDMARD is suddenly discontinued (potentially inflating treatment effect) is underlined. According to the study protocol, exclusion criteria include: 1) Prior treatment B-cell depleting agents within 6 months prior to Day 1 and 2) Use of non-cell depleting bDMARDs within 4 weeks prior to Day 1. Although any loss of partial bDMARD-response is probably similarly distributed in all three treatment groups (due to randomization) and thus it would be expected that the three treatment groups would be equally affected, the applicant was at Day 120 asked to discuss the issue and whether observed treatment effects could have been inflated. In response to the question, the applicant stated that although withdrawal of prior bDMARD therapy could have resulted in a worsening of disease, withdrawal was mandated uniformly in all treatment groups for subjects who failed 1 or more bDMARDs, were intolerant to bDMARDs, or used specific bDMARDs. A majority of the subjects had a longer washout period than what was required by the protocol and that there was no meaningful imbalance noted that would introduce significant bias favouring filgotinib over placebo. Tabulated data that support this statement was provided. Based on this, the CHMP agreed that the risk that residual response of prior bDMARD would potentially inflate the treatment effect and introduce bias favouring filgotinib, is low.

FINCH 3 is an active-controlled study that included a first line population (limited or no prior treatment with MTX) with at least one poor prognostic factor that were randomized to either Filgotinib 100 mgx1+MTX, Filgotinib 200 mgx1+MTX, Filgotinib 200 mgx1 monotherapy or MTX monotherapy with a rescue-possibility (to SOC) at week 24. Overall, the study design and choice of MTX as a comparator are in line with relevant guidelines. However, the two following issues require some additional consideration:

First, antimalarials are included among the permitted concomitant medications and thus the treatment arm referred to as the Filgotinib monotherapy arm is actually not a monotherapy arm in the strictest

sense. As in total, only 9.4% had concurrent antimalarials, since this use has a fairly even distribution among treatment groups and since the treatment effect of antimalarial DMARDs is known to be rather modest, this condition is not expected to have any major impact on the overall study results. However, to verify this preliminary view and to get a more precise view of the performance of Filgotinib given as true monotherapy (which is important given the proposed wording of the indication) the applicant was requested to re-analyse the data with regards to the primary and key secondary endpoints excluding subjects on concomitant anti-malarias (see outcome and discussion below).

Second, as stated in the relevant EMA RA guidelines, for studies on the treatment on naïve patients, remission at 3 or 6 months is the preferred endpoint. The outcome of this endpoint should be corroborated by the other outcomes such as CDAI. In FINCH 3, the proportion of subjects who achieved remission defined as DAS28(CRP) < 2.6 at Week 24 was included as a secondary, ranked endpoint and special consideration will be given to the outcome of this endpoint as it is considered the most relevant for the study population. CDAI was measured in the study and the outcome of this endpoint will also be given extra attention.

Statistical considerations

All the three phase 3 studies, FINCH1, FINCH2 and FINCH3 were run in parallel and shared a number of features implying similarities in the planned statistical analyses that overall are considered appropriate but which required clarifications for a few minor issues. For all three studies, there were two SAPs based on different regional regulatory feedback foremost concerning differences in mutual importance of endpoints, analysis time-points and treatment comparisons. In all three phase 3 studies multiple comparison were planned given the two dose arms of filgotinib and, in one study (FINCH1) due to two comparators, besides placebo also adalimumab. In addition, a number of key secondary endpoints (same but for mTSS in the shorter 24-week study (FINCH2)) were defined and several hypotheses were thereby included in the confirmatory testing hierarchy. This approach was agreed by the CHMP. A comment in the CHMP scientific advice (EMA/CHMP/SAWP/209886/2016) concerned the importance of a hierarchy that could be justified based on clinical relevance. In SAP 2 (EMA), the hierarchy implied that the 200 mg dose was tested first for the primary and key secondary endpoints before the testing of the 100 mg dose commenced. Within the same scientific advice procedure, the non-inferiority comparison versus adalimumab (Study 417-0301/FINCH-1) was criticised with regard to the proposed retention method. The Applicant retained this method and thereby there was no unambiguous definition of the NI margin, no clinical rational offered and no discussion clarifying expected DAS28 (CRP)$\leq$3.2 response rates at week 12 more than expected to be similar in the filgotinib and adalimumab arm, respectively. However, with the primary analysis already performed this is now a matter of assessment (see below)..

In all three phase 3 studies, one primary (composite) and one secondary (treatment policy) estimand were defined that each were aligned with one of two datasets; on-treatment data and all available data, respectively. In primary analyses the data set comprised only data collected while the subject was on randomised treatment ignoring any data collected after the occurrence of an intercurrent event. Intercurrent events where defined as intake of SOC medications due to inadequate response, study treatment discontinuation and study discontinuation. For the primary composite estimand the occurrence of an intercurrent event was taken to be a component of the variable, here implying that for a subject to be a responder for the primary endpoint (ACR20), besides a successful clinical outcome was required not to have discontinued randomised treatment. For secondary analyses, the data set comprised all available data i.e. also measurements observed after a subject had discontinued randomised treatment but stayed in the study on standard of care (instead ignoring the occurrence of an intercurrent event). Albeit both approaches are of interest for an assessment of robustness, it could be questioned whether the primary estimand is equally relevant irrespective of comparison (placebo, adalimumab (FINCH1)) and objective

(superiority or non-inferiority). Analyses using both estimand strategies were pre-planned and have been performed for the primary as well as all key secondary endpoints. However, being difficult to compare the outcomes of the different analyses offered, additional tables showing the outcomes from the analyses based on the two data sets were requested for all three phase 3 studies. In their response to D120 LoQ, the applicant stated that week 52 data were used for the requested analysis. No new analyses were requested but easily digestible summaries of the different analyses performed for the primary analysis of each study respectively. It is assumed that outcomes currently provided are the same as in the original analysis. In comparing outcomes using the on-treatment data approach with the all-available data, the latter ignoring SoC, no concern was raised what regards the already drawn conclusions concerning the efficacy of treatment with filgotinib. Overall, there were generally only minor differences in point estimates and/or CIs and none that alters any conclusion *per se*. The presentation of outcomes based on on-treatment data in the Section 5.1 of the SmPC was therefore accepted by the CHMP.

In the analyses of efficacy endpoints, stratification factors were included as covariates in the analysis. This was agreed by the CHMP. However, if there were discrepancies between the IWRS and the clinical database, the values recorded in the clinical database were to be used in the analyses that hence, not necessarily reflected randomisation restrictions. Being unclear whether there were any discrepancies, the applicant was requested to clarify and, if there were discrepancies for a non-negligible proportion of subjects, provide additional analyses using values according to IWRS. As clarified by the applicant, there were some small discrepancies in stratification factors between the interactive web response system (IWRS) and the clinical database. The proportions in each study has been described. As clear from now presented point estimates for the primary endpoint (ACR20) in all three studies comparing analyses using values according to IWRS and the clinical database respectively, none of the discrepancies seemed to have any impact on the outcomes.

For categorical endpoints, including the primary (ACR20) and e.g. DAS28(CRP) endpoints, a logistic regression analysis with treatment groups and stratification factors in the model was used for statistical inference. For the estimation of treatment differences for e.g. ACR20, the non-stratified response rate difference along with corresponding 95% CI were provided. While acceptable that inference and estimation can be based on different tests/analysis methods, here this implied that the stratification factors were considered in analyses for inference however not for the estimation of the treatment effect. A comparison of outcomes from both adjusted and unadjusted logistic regression models as well as SAS outputs were requested to comprehend the impact of the stratification variables on estimated treatment differences. No clear justification was provided for the approaches using different methods for inference and estimation, but the applicant's answer is interpreted as a wish to avoid odd ratios in the presentation of filgotinib treatment efficacy. The CHMP agreed that results overall, adjusted compared to unadjusted outcomes, were very similar with hence only minor differences, generally in favour of adjusted analyses. Given this and convincing p-values, importantly, overall conclusions are the same (irrespective of analysis).

The main analyses of the primary endpoint followed a "NRI" (Non-responder Imputation) approach in the studies. In case collected data for the primary efficacy assessment was insufficient to calculate ACR20, observations were imputed as non-responders.

- FINCH 1: there were 40/475 patients with imputed response due to missing outcomes data in the placebo arm, vs. 20/475 in the filgotinib 200 mg, 27/480 in the filgotinib 100 mg, 15/325 in the adalimumab arm.
- FINCH 2: there were 21/148 patients with imputed response due to missing outcomes data in the placebo arm, vs. 11/147 in the filgotinib 200 mg and 13/153 in the filgotinib 100 mg arm.

- FINCH 3: it was more balanced in FINCH 3: 47/417 in the placebo arm, vs. 43/416 in the filgotinib 200 mg + MTX arm, 18/207 in the filgotinib 100 mg + MTX arm, 25/210 in the filgotinib 200 mg monotherapy arm.

Overall, in order to appreciate the risk of estimate biases, the Applicant was asked to further discuss the imputed observations in the analysis of primary ACR20 in studies FINCH 1, FINCH 2 and FINCH 3. In most cases, the missing responses corresponded in fact to patients who discontinued treatment prematurely; this was more frequent in the control groups across the studies. Only few evaluable patients had missing ACR assessment across randomization arms (incomplete or completely missing). Taken together, there is no concern what regards a risk that the imputation introduced any important bias.

Efficacy data and additional analyses

Data from the phase II studies; dose response studies

In GLPG0634-CL-201 (MTX add-on), 36 MTX-IRs subjects were randomized. At Week 4, the number and percentage of ACR20 responders (the primary efficacy endpoint) was 4 (33.3%), 9 (75.0%), and 11 (91.7%) in the placebo, Filgotinib 200 mgx1 and the Filgotinib 100 mgx2 groups, respectively.

In GLPG0634-CL-202 (MTX add-on), 91 MTX-IRs subjects were randomized and received study treatment. At Week 4, the percentage of subjects achieving ACR20 response (the primary endpoint) in the placebo group was 41.2% and in the Filgotinib 30 mg/day, Filgotinib 75 mg/day, Filgotinib 150 mg/day and Filgotinib 300 mg/day groups: 35.3%, 54.5%, 40.0%, and 65.0%, respectively.

In GLPG0634CL203; DARWIN 1 (MTX add-on), 594 subjects were randomized and treated. The outcome of the primary endpoint, ACR 20 response at week 12, was: 44.2% in the placebo group, 56.1% in 50 mgx1 group, 63.5% in the 100 mgx1 group, 68.6% in the 200 mgx1, 57.0% in the 25 mgx1 group, 60.0% in the 50 mgx2, 78.6% in the 100 mgx2 group (p-values<0.05 for the comparison vs placebo for the 100 mgx1, 200 mgx1 and 100 mgx2 groups). Dose-dependent responses were observed in the majority of these secondary efficacy parameters including proportion of subjects achieving remission/LDA. It is noted that the level of response with regards to the primary endpoint was different in the four investigated regions and tended to be lower in EU than in the other three regions. However, as the effect size vs placebo was comparable in the 4 regions, the issue was not further pursued by the CHMP.

In GLPG0634-CL-204; DARWIN 2 (monotherapy study), 283 subjects were randomized and treated. It is noted that according to the inclusion criteria, eligible subjects had to have shown an inadequate response in terms of either lack of efficacy or toxicity to MTX but according to the presented baseline data, only 84.1 % had prior use of MTX and 7.8% had prior use of MTX sodium. However, 97.5 % had previous treatment with csDMARD which means that this is still a representative second line population.

The outcome of the primary endpoint, ACR 20 response at week 12, was: 29.2% in the placebo group, 66.7% in the 50 mgx1 group, 65.7% in the 100 mgx1 group and 72.5% in the 200 mgx1 group (p<0.0001 for all comparisons vs placebo). The level of response with regard to the primary endpoint was different in the four investigated regions and tended to be lower in EU than in the other three regions, however the effect size vs placebo was similar in the 4 regions.

The outcome for the secondary endpoint DAS28 (CRP) remission or LDA at Weeks 12 (NRI [ITT Population]) was as follows at week 12: 13.9% (10/72) in the placebo group, 23.6% (17/72) in the 50 mgx1 group, 27.1% (19/70) in the 100 mgx1 group and 44.9% (31/69) in the 200 mgx1 group (p-value<0.05 for the comparison of the 200 mg group vs placebo). At week 24 the proportion with

DAS28 (CRP) remission or LDA was 34.7% in the 50 mgx1 group, 50.0% in the 100 mgx1 group and 42.0% in the 200 mgx1 group.

In response to the Day 120 LoQ, a re-analyse of important endpoints in DARWIN 2 excluding subjects concomitant antimalarials were conducted. The outcome in all study subjects vs subjects without antimalarials (FAS, NRI) were compared. The proportion of subjects with LDA at week 12 was similar in the three different treatment groups (Filgotinib 200 mg, Filgotinib 100 mg, placebo) for all subjects vs subjects without antimalarials. Such coherence was seen also for the other presented endpoints including ACR 20, which was the primary efficacy endpoint of this study and remission. The CHMP agreed with the applicant that the results in this monotherapy second line study were similar for subjects without antimalarials as compared to the overall study population.

Following the phase II studies, the applicant had initially selected only the 200 mgx1 dose to be tested in the phase 3 programme. As this was questioned by the SAWP/CHMP, both the 100 mg once daily and 200 mg once daily-doses were then ultimately chosen for the phase 3 studies. Overall, treatment with these doses conferred a clinically relevant effect vs placebo in the studied MTX-IR (second line) population both in the MTX add-on and monotherapy setting. Given the clinical efficacy data (including the dose-response observed) and the clinical safety data from this phase 2 studies, the selection of doses is considered acceptable. Of note, this would provide some support for the efficacy of filgotinib as monotherapy second line.

From the week 156- interim CSR of GLPG0634-CL-205; DARWIN 3, the long term follow-up that included subjects that received filgotinib monotherapy (n = 242, rolled over from parent study DARWIN 2) or filgotinib with MTX (n = 497, rolled over from parent study DARWIN 1), there are indications that the treatment effect of filgotinib (as monotherapy or in combination with MTX) is maintained for up to 3 years in patients. The majority of subjects were on 200 mg Filgotinib/day. It is noted that 229/491 MTX-IR subjects in the MTX + Filgotinib group had low disease activity at baseline and 200/290 subjects had low disease activity at week 156. For the monotherapy group, the numbers were 97/234 and 88/136. This is, together with the week 52 phase III data (see below), considered consistent with maintenance of efficacy.

Data from the phase III studies; main studies

In GS-US-417-0301, FINCH 1, the second line MTX-add on study, 1755 subjects were randomized and treated. All superiority or noninferiority tests of filgotinib versus comparator in the hierarchical testing demonstrated a statistically significant superiority or noninferiority of filgotinib over the comparator ($p < 0.001$), with the exception of the final noninferiority test of the percentages of subjects who achieved DAS28(CRP) $\leq$ 3.2 at Week 12 (filgotinib 100 mg vs adalimumab; $p = 0.054$). Non-inferiority of Filgotinib 200 mg vs adalimumab (for DAS28(CRP) <= 3.2 at Week 12) was confirmed also in the Per-Protocol analysis.

For the primary endpoint, ACR 20 at week 12, the proportion of responders were 76.6% in the Filgotinib 200 mgx1 (+MTX) group, 69.8% in the Filgotinib 100 mgx1(+MTX) group, 70.8% in the Adalimumab(+MTX) group and 49.9% in the placebo(+MTX) group ($p<0.001$ for both superiority comparisons between the Filgotinib groups and the placebo group). For the key secondary endpoint of special regulatory interest, LDA at week 12, the proportion of responders were 49.7% in the Filgotinib 200 mgx1 (+MTX) group, 38.8% in the Filgotinib 100 mgx1(+MTX) group, 43.4% in the adalimumab (+MTX) group and 23.4% in the placebo (+MTX) group ($p<0.001$ for both superiority comparisons between the Filgotinib groups and the placebo group). The differences for the Filgotinib groups vs placebo for these endpoints were both statistically significant and clinically relevant.

Across endpoints, the short-term effect in the Filgotinib 200 mgx1 group (on top of MTX) was consistently numerically better than in the other treatment groups (Filgotinib 100 mgx1, adalimumab or placebo on

top of MTX). This was noted for the proportion of subjects that achieved remission and disease activity, the most informative endpoints in this patient population, and for the radiological endpoint included among the key secondary endpoints (change from Baseline in mTSS). Numerically better improvements in the Filgotinib 200 mg group vs the other groups were finally seen for PROs and the CRP-independent outcome CDAI that were included as other endpoints in the study. Overall, not only the effect in the Filgotinib group 200 mgx1 (+MTX) group but also the effect in the Filgotinib 100 mgx1 (+MTX) group is of clinical relevance. There was a consistent and distinct difference for the Filgotinib 100 mgx1 (+MTX) group vs placebo (+MTX) and overall the observed magnitude of effect in the Filgotinib 100 mg (+MTX)-group was similar to what was observed in the active comparator adalimumab (+MTX) group.

The outcome with regards to the primary endpoint in FINCH 1 is largely consistent with the outcome in the phase IIb study DARWIN 1 which also included MTX-IRs and was a MTX add-on study.

For the interpretation of the subgroup analysis, it should be noted that randomization was stratified by geographic region, prior exposure to biologic disease modifying antirheumatic drugs (bDMARDs), and presence of RF or anti-CCP at screening. Compared to placebo, a beneficial effect of Filgotinib was seen across the investigated subgroups with regards to achievement of the primary endpoint, although there were some differences regarding for example the efficacy in seropositive vs seronegative, BMI, race and geographic region. The outcome of the subgroup analysis of the key secondary endpoints which was provided in the response to the D120 LoQ, overall supported the conclusion of consistent treatment effect.

Taken together, the observed short-term efficacy of both the studied doses of filgotinib on top of MTX in the MTX-IR population are of clear clinical relevance and of similar magnitude as the effect of the active comparator adalimumab. Depending on the safety profile of Filgotinib, both the tested doses could be considered for the finally recommended posology (currently, the applicant proposes 200 mgx1 as the primary posology, reserving 100 mgx1 for patients with reduced renal function). The part of the proposed indication covering second line treatment in combination with MTX can be considered supported by the submitted data.

Regarding long-time efficacy, at week 24, the number of ACR 20 responders in absolute numbers increased vs week 12 in all groups but in particular in the placebo group. This was true also for the numbers of subjects that achieved DAS28 (CRP) <2.6 and DAS28 (CRP) <= 3.2 at week 12 vs week 24.

In response to the D120 LoQ, it was reported that the absolute number of responders in the Filgotinib 200 mg-group did not decrease from week 24 to week 52. For the Filgotinib 100 mg group and the adalimumab group, a similar pattern was seen. The ACR 20 response increased among placebo subjects that subsequently received Filgotinib. For LDA, the absolute number of responders increased in all treatment groups through week 12-24-52. Also with regards to remission, the absolute number of subjects increased from week 24 to week 52 in all three active treatment groups. It was clarified that for subjects who discontinued study drug and received standard of care, their efficacy data collected after receiving standard of care (from Week 14 and onwards) were excluded and treated as missing and missing binary efficacy data were imputed as non-responders.

The applicant also showed that in all groups, a step up in ACR20 response from Week 12 to Week 14 was observed. This step up was larger in the placebo group compared with the active treatment groups. Week 14 was the first time point that blinded study drug had to be discontinued for subjects with an inadequate response, as defined in the protocol. The applicant states that as both subjects and investigators were aware of the requirement to discontinue blinded study drug, there may have been a bias toward reporting higher response rates and that this potential bias (which according to the applicant has been observed in other clinical studies) may have contributed to the placebo rate being higher at Week 24 compared with Week 12.

Taken together, the CHMP agreed that treatment efficacy of Filgotinib is maintained on a group-level for up to 1 year for both Filgotinib doses as add-on to MTX in the MTX-IR population in FINCH 1. Efficacy even appeared to improve not only from week 12 to week 24 but also from week 24 to week 52 which is unexpected. It is further noted that the proportion of ACR 20 responders in the adalimumab (+MTX) arm is somewhat higher than expected (and reported for adalimumab + MTX in the adalimumab PI) but in particular the proportion of ACR 20 responders in the placebo group at week 12 and 24 are higher than what would have been expected. However, as there is a clear difference for Filgotinib vs placebo at all timepoints and (at least) comparable effect to adalimumab, as there was a clear increase in the number of responders after the placebo subjects had been re-randomized to Filgotinib at week 24 and as the outcome in the comparator arms are clearly presented in the SmPC along with the outcome in the Filgotinib arms, this issue was not further pursued by the CHMP.

Finally, in response to the RSI, radiological measurements up to week 52 were provided and are reflected in the approved product information.In GS-US-417-0302, FINCH 2, the third line csDMARD-add on study, 448 subjects were randomized and treated. Filgotinib 200 mgx1 (+csDMARD) or 100 mgx1 (+ csDMARD) showed superiority over placebo (+csDMARD) for the primary endpoint and all key secondary endpoints. The outcome for the LDA-endpoint is of particular importance and there was a clear and clinically relevant difference between Filgotinib (both the high and low dose) vs placebo for this endpoint. Also, for the CRP/ESR-independent endpoint CDAI differences for Filgotinib vs placebo were noted. Overall, 15.0% discontinued the study prematurely with the highest number in the placebo group and lowest number in the Filgotinib 200 mg group. This imbalance is not expected to change the main, clearly positive, outcome of the study; at least not the outcome of the primary and key secondary endpoints assessed at week 12, a timepoint at which a higher number were still in the study (only about 10% of the number in the primary analysis appears to have been imputated while 90% were observed).

The proportion that attained the primary endpoint, ACR 20 at week 12, was 66.0% in the Filgotinib 200 mgx1 (+csDMARD) group, 57.5% in the Filgotinib 100 mg (+csDMARD) group and 31.1% in the placebo (+csDMARD) group ($p<0.001$ for both the comparison between the Filgotinib groups and placebo). For the secondary endpoint of special regulatory interest, proportion of subjects who achieved DAS28(CRP) $\leq$ 3.2 at Week 12, it was 40.8% in the Filgotinib 200 mgx1 (+csDMARD) group, 37.3% in the Filgotinib 100 mgx1 (+csDMARD) group and 15.5% in the placebo (+csDMARD) group ($p < 0.001$ for both comparisons with placebo).

Consistently, the results in the Filgotinib 200 mg arm were numerically better than in the Filgotinib 100 mg arm but the differences were not large. Relevant differences vs placebo was seen for both doses with regards to ACR response and LDA as presented above but also with regards to function as measured by HAQ and the ESR/CRP-independent measure CDAI. Consequently, the CHMP considered that both Filgotinib doses could be included in the recommended primary posology.

Numerically better improvements were seen Filgotinib vs placebo for primary and key secondary endpoints from week 2-4 through week 24. In all three groups, the absolute number of subjects that was considered as responders with regards to the primary study endpoint was roughly similar week 24 compared to week 12. However, in GS-US-417-0302 / FINCH 2, maintenance of effect beyond 24 weeks could not be demonstrated and such evidence, as well as data on radiographic progression, needs to come from other studies in the development programme.

Filgotinib appears effective across subgroups with regards to promoting ACR 20 response. Randomization was stratified by the number of bDMARDs: < 3 or ≥ 3 (as well as region and positive serology) and ACR 20 responses at week 12 were similar in these two subgroups. This is important considering the discussion in the previous SA. It is further noted that also the proportion of subjects that achieved LDA at week 12 was similar in subjects exposed to < 3 or ≥ 3 bDMARDs.

Compared to placebo, a beneficial effect of Filgotinib was seen across analysed subgroups with regards to achievement of the primary endpoint although there were some differences regarding for example the efficacy in seropositive vs seronegative, BMI, race and geographic region. In the response to the D120 LoQ, the applicant conducted additional subgroup analyses addressing previous treatment experience and based on this it can be concluded that the effects of filgotinib appear consistent regardless of MoA and number of prior exposures to bDMARDs. There was a numerical difference vs placebo in all analysed subgroups. The efficacy of filgotinib was further evaluated in subjects with bDMARD intolerance compared with the overall subject population using ACR20 at Week 12, and DAS28(CRP) < 2.6 and DAS28(CRP) ≤ 3.2 at Weeks 12 and 24. Although small differences were observed, the efficacy in this subgroup appeared generally similar to the outcome in the overall population. The intolerant group constituted only 103/448 subjects in the FAS (23%) limiting the impact of the outcome in this subgroup on the result in the overall population.

The conclusion that Filgotinib has a beneficial effect across the entire (in some respects) heterogeneous study population, was overall supported by the outcome in the different baseline factor subgroups that was provided for all key endpoints in the FINCH 2 study with the responses to the D120 LoQ.

In conclusion, the results overall indicate that Filgotinib given on top of csDMARDs to bDMARD-IR subjects are clearly better than placebo and the effect is observed from week 2-4 to week 24.

It is noted that GS-US-417-0302 / FINCH 2 is essentially the only study in the clinical development programme for Filgotinib designed to provide efficacy data for Filgotinib on top of csDMARD (i.e. not only on-top of MTX). The setting of this study is third line. Permitted csDMARDs included MTX, hydroxychloroquine, sulfasalazine, leflunomide. However, a clear majority in this study was treated with MTX (84.4% in Filgotinib 200 mg, 83.0% in Filgotinib 100 mg and 78.4% in the placebo group). The efficacy data from this study is considered supportive of the part of the indication that consists of combination therapy third line.

In GS-US-417-0303; FINCH 3, the first line study, 1249 subjects were randomized and treated. On average the included subjects had high disease activity as measured by DAS28 CRP (DAS28-CRP >5.1) and most patients (>90%) had at least one erosion.

FINCH 3 met its primary endpoint demonstrating the superiority of filgotinib 200 mg + MTX over MTX monotherapy on the ACR20 response rate at Week 24. Moreover, Filgotinib 200 mg + MTX and Filgotinib 100 mg + MTX demonstrated superiority over MTX monotherapy for ACR20, HAQ-DI, and DAS28(CRP) < 2.6 at Week 24. The formal sequential testing according to SAP 2 was stopped at step 7 and only nominal significance was reported for the remaining hypotheses. However, numerically lower radiographic progression from baseline was observed in the mTSS at week 24 for the filgotinib 200 mg + MTX, filgotinib 100 mg + MTX and filgotinib 200 mg monotherapy groups compared with the MTX monotherapy group. Numerically higher improvements for the ESR/CRP-independent outcome-measure CDAI in the three Filgotinib groups vs the MTX monotherapy group were also noted.

With regards to the primary endpoint, ACR 20 response at week 24, this was reached by 81.0% in the Filgotinib 200 mgx1+MTX group, 80.2% in the Filgotinib 100 mg x1+MTX group, 78.1% in the Filgotinib 200 mg monotherapy group and 71.4% in the MTX monotherapy group ($p<0.05$ for the two comparisons between Filgotinib combination therapy vs MTX). For the secondary endpoint of special interest, proportion with DAS28(CRP) < 2.6 (remission) at Week 24, this was achieved by 54.1% in the Filgotinib 200 mg 1x1 + MTX group, 42.5%, in the Filgotinib 100 mg 1x1+MTX, 42.4% in the Filgotinib 200 mg monotherapy group and 29.1% in the MTX monotherapy group ($p < 0.001$ for the comparisons with the two Filgotinib combination groups and MTX monotherapy group respectively). The proportion of ACR 20 responders at week 24 were indeed numerically higher in all Filgotinib treatment arms compared to MTX monotherapy but the differences were not large between any of the arms in the study. However, with regards to the more relevant endpoint proportion of subjects in remission (DAS28 CRP<2.6) at week 24,

the magnitude of the difference between the arms were larger (Filgotinib high dose + MTX vs low dose +MTX or high dose monotherapy as well as Filgotinib monotherapy vs MTX monotherapy) and considered clinically meaningful.

Numerically greater ACR20 response rates versus MTX monotherapy were seen from Week 2 for the Filgotinib groups and through Week 24. This was observed also for the proportion of subjects in remission (DAS28 CRP<2.6).

It is noted that there were 50 additional ACR 20 responders from week 12 to week 24 in the MTX-group which is of interest as individual response to MTX treatment is usually assessed at 3-4 months. The increase in ACR 20 response between week 12 and 24 was not as prominent in the Filgotinib arms. Regarding the number of subjects that achieved DAS28 CRP<2.6, there was an apparent increase between 12 and 24 weeks for all treatment groups including the MTX-group, in which 50 additional subjects became responders.

In all four treatment groups there was a slight decrease in the absolute number of ACR 20 responders from week 24 to week 52. In the Filgotinib + MTX arms, the absolute number in remission were essentially the same week 24 and week 52 while it increased somewhat from week 24 to week 52 in the Filgotinib mono-arm and the MTX arm. The latter observation is unexpected but as there is a clear difference for the Filgotinib groups vs the MTX group at both timepoints, the issue will not be further pursued. Overall, it is agreed that treatment efficacy is maintained on a group-level for up to 1 year for both Filgotinib +MTX (in the two tested doses), Filgotinib 200 mg monotherapy and MTX monotherapy in the MTX naïve patients in FINCH 3.

In response to questions to the CHMP, radiological measurements up to week 52 were provided. At Week 52, a numerically greater proportion of subjects in the filgotinib 200 mg + MTX group had no radiographic progression compared with the MTX monotherapy group.

Overall, there were no unexpected findings in the subgroup analysis or the sensitivity analysis. When interpreting the subgroup analysis, it should be noted that randomization was stratified by geographic region and presence of either RF or anti-CCP. Compared to MTX monotherapy, a beneficial effect of Filgotinib measured as ACR 20 seemed to be present across the investigated subgroups although some differences with regards to for example seropositivity, BMI, region, race and age were noted. The outcome in the different baseline factor subgroups for all key endpoints, which was provided as a response to the D120 LoQ, supported the conclusion of overall consistency of treatment effect.

The applicant was asked to re-analyse the data in subjects without antimalarials with focus on Filgotinib monotherapy. The proportion of subjects that achieved the primary endpoint, ACR 20 at week 24 were in the Filgotinib 200 mg monotherapy group 78.1% for all subjects vs 77.2% for subjects without antimalarials. Also in the other three treatment arms in the study, the differences in outcome between the overall population and subjects without antimalarials were very marginal. As for the proportion that achieved remission according to DAS28 at week 24, it was 42.4% for all subjects and 43.0% for subjects without antimalarials in the Filgotinib 200 mg monotherapy group. Also in the other three treatment arms, the differences in outcome between the overall population and subjects without antimalarials were marginal (and not better in the "all subject"-group). Similar patterns were seen also for the other presented endpoints. Thus, the CHMP agreed with the applicant that the results in this monotherapy first line study were similar for subjects without antimalarials as compared to the overall study population.

In conclusion, a preliminary view is that the combination of Filgotinib + MTX achieved better efficacy in a MTX-naïve population than MTX alone from week 2 to week 24.

The currently proposed indication includes monotherapy ≥second line. Support for monotherapy second line could come from DARWIN 2. However, for monotherapy ≥third line, there are no observed data and thus this part of the indication will instead have to rely on extrapolation. It should be noted that previously

approved JAK-inhibitors (baricitinib and tofacitinib) that are indicated for use in monotherapy third line were also evaluated only as combination therapy in this setting. It is further noted that placebo-corrected response rates for ACR 20 and LDA appear similar for combination therapy 3rd line (FINCH 2) vs combination therapy 2nd line (FINCH 1). Although the limitations of inter-study comparisons are acknowledged, this provides some support for the extrapolation of efficacy observed with monotherapy 2nd line to monotherapy 3rd line. Taking into account the totality of data supporting the efficacy of Filgotinib therapy in RA, it is considered that, in line with previous precedents, there is no absolute requirement for separate monotherapy data third line to approve this part of the indication.

With regards to the observed monotherapy data, the following observations can be made:

-Regarding monotherapy first line: Although data are somewhat limited and although none of the comparisons between filgotinib 200 mg monotherapy and MTX in FINCH 3 resulted in an outcome that was considered statistically significant, it is noted that for the primary endpoint and all three key secondary endpoints (which included effect on structural progression and function as well as proportion of subjects in remission) numerically better outcomes were noted for filgotinib monotherapy vs MTX monotherapy (the active comparator). However, the CHMP questioned the initially proposed monotherapy indication in the D120 LoQ in the light of the totality of data on JAK-inhibitors that has so far become available also considering that such indication has not been approved for previous members in the class. As a consequence, the first line indication was withdrawn by the applicant during the application.

-Regarding monotherapy second line: In the phase 2 DARWIN 2-study, an effect of filgotinib 200 mg vs placebo was seen both for the primary and the secondary endpoints (including the proportion of subjects with remission/low disease activity). Although an active comparator would have been a more appropriate choice than placebo to better elucidate the effects of monotherapy in this MTX-IR population, the study included a rather limited number of patients and did not include a direct comparison between filgotinib monotherapy vs. filgotinib in combination, this data provides some support for monotherapy second line. Together with the support that can be retrieved through extrapolation from FINCH 3, data from DARWIN 3 (that supports maintenance of effect of filgotinib monotherapy second line although only pooled data from this study was provided without details on the exact dose regimen in each group), it is considered sufficient to support the proposed monotherapy second line indication as it is currently worded (i.e. with no restrictions that monotherapy second line is only indicated when combination therapy is inappropriate- as the available data do not indicate a major efficacy advantage for the combination vs monotherapy and there are instead safety disadvantages associated with the combination, see safety section 2.6.).

2.5.4. Conclusions on the clinical efficacy

In conclusion, the CHMP considered that the data submitted by the Applicant support the short-term efficacy of Filgotinib, both as monotherapy and in combination with MTX for the treatment of RA second and third line. Data supporting maintenance of effect up to 1 year has also been provided.

However, the CHMP questioned the initially proposed indication "*[Tradename] is indicated as monotherapy for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have highly active and early progressive (erosive) disease, were not previously treated with MTX, and for whom treatment with MTX is inappropriate"* in the D120 LoQ in the light of the data submitted with this application, the totality of data on JAK-inhibitors that has so far become available and also considering that it would be the 1st in the class. The first line indication was withdrawn by the applicant with their responses to the D120 LoQ (see also Section 2.6.1).

In addition, filgotinib was initially proposed to be given either in monotherapy or in combination with MTX or other csDMARDs. Since sufficient data supporting the combination with csDMARDs other then MTX

were not presented, this was raised as a major objection in the D120 LoQ. As a consequence, the proposal for use in combination with csDMARDs was withdrawn by the applicant with their responses to the D120 LoQ.

In conclusion, the application is considered acceptable from an efficacy perspective in the revised indication:

"*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).*"

2.6. Clinical safety

Patient exposure

A total of 4120 subjects with RA have received at least 1 dose of filgotinib for a total exposure of 7218.36 patient-years of exposure (PYE) across all Phase 2 and Phase 3 RA studies. Of these, 2928 subjects have received any dose of filgotinib for over 1 year (PYE = 6647.91).

Table 20 presents an overview of studies that provide safety data for the Pooled Phase 2 and Phase 3 Safety Population.

Table 20. Studies Included in the Pooled Safety Population

Study	Study Design	Treatment Regimens	Number of Subjects	Subject Population	Database Finalization Dates
GS-US-417-0301 (FINCH 1)	Phase 3, randomized, double-blind, placebo- and active-controlled study	Filgotinib 200 mg, QD; filgotinib 100 mg, QD; adalimumab 40 mg SC, Q2W; or placebo for up to 52 weeks. Subjects were on a stable dose of 7.5 to 25 mg MTX/week.	1755	Adult subjects with moderately to severely active RA; MTX-IR	08 October 2018 (original MAA)/ 22 July 2019 (final analysis)
GS-US-417-0302 (FINCH 2)	Phase 3, randomized, double-blind, placebo-controlled study	Filgotinib 200 mg, QD; filgotinib 100 mg, QD; or placebo for up to 24 weeks. Subjects were taking a stable dose of 1 to 2 permitted csDMARDs.	448	Adult subjects with moderately to severely active RA; bDMARD-IR	24 August 2018
GS-US-417-0303 (FINCH 3)	Phase 3, randomized, double-blind, placebo- and active-controlled study	Filgotinib 200 mg QD and MTX up to 20 mg QW; filgotinib 100 mg QD and MTX up to 20 mg QW; filgotinib 200 mg QD monotherapy; or MTX monotherapy up to 20 mg QW for up to 52 weeks.	1249	Adult subjects with moderately to severely active RA; MTX-naive	08 October 2018 (original MAA)/ 22 July 2019 (final analysis)
GS-US-417-0304 (FINCH 4)	Phase 3, double-blind, long-term extension study	Filgotinib 200 mg QD or filgotinib 100 mg QD for up to 6 years.	2729	Eligible subjects who had completed 1 of the 3 parent RA studies (GS-US-417-0301, GS-US-417-0302, or GS-US-417-0303)	08 October 2018 (original MAA)/ 16 September 2019
GLPG0634-CL-203 (DARWIN 1)	Phase 2b, randomized, double-blind, placebo-controlled, dose-finding, add-on study	Filgotinib 25 mg BID; filgotinib 50 mg QD; filgotinib 50 mg BID; filgotinib 100 mg QD; filgotinib 100 mg BID; filgotinib 200 mg QD; or placebo BID for up to 24 weeks Subjects were on a stable dose of 15 to 25 mg MTX/week.	Total: 594 Pooled Phase 2/3 Safety Population: 276[a]	Adult subjects with moderately to severely active RA; MTX-IR	25 June 2015
GLPG0634-CL-204 (DARWIN 2)	Phase 2b, randomized, double-blind, placebo-controlled, monotherapy, dose-finding, study	Filgotinib 50 mg QD; filgotinib 100 mg QD; filgotinib 200 mg QD; or placebo QD for up to 24 weeks.	Total: 283 Pooled Phase 2/3 Safety Population: 226[a]	Adult subjects with moderately to severely active RA; MTX-IR	07 July 2015

Study	Study Design	Treatment Regimens	Number of Subjects	Subject Population	Database Finalization Dates
GLPG0634-CL-205 (DARWIN 3)	Phase 2, open-label, multicenter, long-term extension study	Filgotinib 200 mg QD, filgotinib 100 mg BID, or filgotinib 100 mg QD (US males) for approximately 96 months Subjects could be switched to filgotinib 100 mg QD when deemed necessary by the investigator. Subjects may have been on a stable dose of MTX.	Total: 739 Pooled Phase 2/3 Safety Population: 487[a]	Eligible subjects who had completed 1 of the 2 parent RA studies (GLPG0634-CL-203 or GLPG0634-CL-204)	30 May 2018 (original MAA)/ 26 April 2019

bDMARD = biologic disease-modifying antirheumatic drug; BID = twice daily; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CSR = clinical study report; IR = inadequate responder; MAA = marketing authorisation application; MTX = methotrexate; Q2W = twice weekly; QD = once daily; QW = once weekly; RA = rheumatoid arthritis; SC = subcutaneous; US = United States

a Subjects in Studies GLPG06343-CL-203, GLPG06343-CL-204, and GLPG06343-CL-205 who received filgotinib 200 mg once daily, filgotinib 100 mg once daily, or placebo (± MTX) were included in the Pooled Phase 2 and Phase 3 Safety Analysis Set.

Source: GS-US-417-0301 Interim Week 24; GS-US-417-0301 Final; GS-US-417-0302; GS-US-417-0303 Interim Week 24; GS-US-417-0303 Final; GS-US-417-0304 Interim 1; GLPG0634-CL-203; GLPG0634-CL-204; GLPG0634-CL-205 Interim 1; and Filgotinib RA MAA ISS Update SAP

Adverse events

Phase 1 studies

Filgotinib has been evaluated in Phase 1 studies in healthy volunteers. Adverse events of interest were not formally evaluated in the healthy volunteer studies. One occurrence of non-serious DVT was reported in a female subject following a single-dose of filgotinib in a healthy volunteer study (Study GS-US-417-3900).

Pooled data from phase 2 and 3 studies

Table 21 presents an overall summary of AEs during the first 12 weeks of treatment for As Randomized Subjects in the Pooled Phase 2 and Phase 3 studies.

Table 21. Overall Summary of Adverse Events in the First 12 Weeks: Pooled Phase 2 and Phase 3 Safety Population (As Randomized Subjects, Safety Analysis Set)

Number (%) of Subjects with Any	Filgotinib			Adalimumab (N=325)	Other (N=1197)
	Filgotinib 200 mg (N=1403)	Filgotinib 100 mg (N=995)	Total (N=2398)		
TEAE	658 (46.9%)	442 (44.4%)	1100 (45.9%)	130 (40.0%)	522 (43.6%)
TEAE with Grade 3 or Higher	53 (3.8%)	39 (3.9%)	92 (3.8%)	13 (4.0%)	39 (3.3%)
TEAE Related to Study Drug	279 (19.9%)	177 (17.8%)	456 (19.0%)	44 (13.5%)	203 (17.0%)
TEAE Related to Study Drug with Grade 3 or Higher	25 (1.8%)	10 (1.0%)	35 (1.5%)	8 (2.5%)	11 (0.9%)
TE Serious AE	34 (2.4%)	27 (2.7%)	61 (2.5%)	9 (2.8%)	21 (1.8%)
TE Serious AE Related to Study Drug	13 (0.9%)	6 (0.6%)	19 (0.8%)	7 (2.2%)	5 (0.4%)
TEAE Leading to Premature Discontinuation of Study Drug	25 (1.8%)	12 (1.2%)	37 (1.5%)	9 (2.8%)	21 (1.8%)
TEAE Leading to Premature Discontinuation of Study	14 (1.0%)	8 (0.8%)	22 (0.9%)	4 (1.2%)	11 (0.9%)
TEAE Leading to Temporary Interruption of Study Drug	103 (7.3%)	71 (7.1%)	174 (7.3%)	16 (4.9%)	79 (6.6%)
TE Death	2 (0.1%)	1 (0.1%)	3 (0.1%)	0	1 (<0.1%)
TE Serious AE Leading to Death	2 (0.1%)	1 (0.1%)	3 (0.1%)	0	1 (<0.1%)

TE = treatment-emergent; TEAE = treatment-emergent adverse event
Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, or other (placebo ± MTX or csDMARDs, and MTX monotherapy). Adverse events were coded according to MedDRA Version 21.0. Severity grades were defined by or converted to the CTCAE Version 4.03. Treatment-emergent events began on or after the first dose date of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, or other, and no later than the earlier date of either 30 days after the last dose date, or the first dose date of the switched treatment minus 1 day. Treatment-emergent death happened on or after the first dose date of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, or other, and no later than the earlier date of either 30 days after the last dose date, or the first dose date of the switched treatment minus 1 day.

Table 22 presents AEs reported for at least 2% of As Randomized Subjects in any treatment group in the PC Safety Analysis Set up to Week 12.

Table 22. Adverse Events Reported for at Least 2% of Subjects in Any Treatment Group Up to Week 12 in the Pooled Safety Population by Preferred Term (Placebo-Controlled Safety Analysis Set, As Randomized Subjects)

Preferred Term	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Placebo (N=781)
	+ csDMARDs (N=708)	Monotherapy (N=69)	Total (N=777)	+ csDMARDs (N=718)	Monotherapy (N=70)	Total (N=788)	
Number (%) of Subjects with Any Treatment-Emergent Adverse Event by Week 12	324 (45.8%)	30 (43.5%)	354 (45.6%)	301 (41.9%)	22 (31.4%)	323 (41.0%)	316 (40.5%)
Nasopharyngitis	27 (3.8%)	0	27 (3.5%)	19 (2.6%)	0	19 (2.4%)	19 (2.4%)
Upper respiratory tract infection	24 (3.4%)	2 (2.9%)	26 (3.3%)	19 (2.6%)	1 (1.4%)	20 (2.5%)	14 (1.8%)
Nausea	25 (3.5%)	2 (2.9%)	27 (3.5%)	17 (2.4%)	1 (1.4%)	18 (2.3%)	13 (1.7%)
Headache	21 (3.0%)	1 (1.4%)	22 (2.8%)	17 (2.4%)	0	17 (2.2%)	16 (2.0%)
Hypertension	16 (2.3%)	1 (1.4%)	17 (2.2%)	12 (1.7%)	0	12 (1.5%)	9 (1.2%)
Urinary tract infection	10 (1.4%)	3 (4.3%)	13 (1.7%)	11 (1.5%)	3 (4.3%)	14 (1.8%)	7 (0.9%)
Bronchitis	10 (1.4%)	0	10 (1.3%)	7 (1.0%)	1 (1.4%)	8 (1.0%)	17 (2.2%)
Cough	7 (1.0%)	2 (2.9%)	9 (1.2%)	7 (1.0%)	0	7 (0.9%)	12 (1.5%)
Rheumatoid arthritis	3 (0.4%)	1 (1.4%)	4 (0.5%)	5 (0.7%)	1 (1.4%)	6 (0.8%)	22 (2.8%)
Constipation	7 (1.0%)	0	7 (0.9%)	8 (1.1%)	2 (2.9%)	10 (1.3%)	7 (0.9%)
Gastroenteritis	6 (0.8%)	2 (2.9%)	8 (1.0%)	4 (0.6%)	0	4 (0.5%)	6 (0.8%)
Dyspepsia	5 (0.7%)	2 (2.9%)	7 (0.9%)	6 (0.8%)	0	6 (0.8%)	3 (0.4%)
Alopecia	7 (1.0%)	2 (2.9%)	9 (1.2%)	4 (0.6%)	0	4 (0.5%)	2 (0.3%)
Hypercholesterolaemia	6 (0.8%)	0	6 (0.8%)	3 (0.4%)	2 (2.9%)	5 (0.6%)	1 (0.1%)
Back pain	5 (0.7%)	1 (1.4%)	6 (0.8%)	1 (0.1%)	2 (2.9%)	3 (0.4%)	3 (0.4%)
Vertigo	5 (0.7%)	0	5 (0.6%)	2 (0.3%)	3 (4.3%)	5 (0.6%)	0
Dyslipidaemia	5 (0.7%)	0	5 (0.6%)	1 (0.1%)	2 (2.9%)	3 (0.4%)	3 (0.4%)
Hypertriglyceridaemia	2 (0.3%)	1 (1.4%)	3 (0.4%)	3 (0.4%)	2 (2.9%)	5 (0.6%)	1 (0.1%)
Neck pain	0	2 (2.9%)	2 (0.3%)	0	0	0	5 (0.6%)
Toothache	1 (0.1%)	0	1 (0.1%)	1 (0.1%)	2 (2.9%)	3 (0.4%)	1 (0.1%)

csDMARD = conventional synthetic disease-modifying antirheumatic drug; MTX = methotrexate; QD = once daily
Placebo-Controlled Safety Analysis Set includes subjects who received at least 1 dose of filgotinib 100 mg once daily (with or without MTX or csDMARDs), filgotinib 200 mg once daily (with or without MTX or csDMARDs), or placebo (with or without MTX or csDMARDs).
Adverse events were coded according to MedDRA Version 22.0.
Treatment-emergent events began on or after the first dose date of filgotinib 100 mg once daily, filgotinib 200 mg once daily, MTX, or placebo, and no later than the earlier date of either 30 days after the last dose date, or the first dose date of the switched treatment minus 1 day.
Multiple AEs were counted only once per subject for each treatment period for each preferred term.

Table 23 presents an overall summary of AEs for As Treated Subjects in the pooled safety population.

Table 23. Overall Summary of Adverse Events in the Pooled Safety Population (Safety Analysis Set, As Treated Subjects)

Number (%) of Subjects with Any	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)			
TEAE	1412 (77.7%)	359 (79.8%)	1771 (78.1%)	1081 (72.4%)	59 (38.6%)	1140 (69.2%)	239 (73.5%)	305 (73.3%)	426 (54.5%)
	47.0 (44.6,49.5)	34.4 (30.9,38.1)	43.8 (41.7,45.8)	55.0 (51.8,58.4)	86.4 (65.8,111.5)	56.1 (52.9,59.4)	82.4 (72.3,93.5)	85.6 (76.3,95.8)	140.9 (127.8,154.9)
TEAE Related to Study Drug	656 (36.1%)	170 (37.8%)	826 (36.4%)	455 (30.5%)	23 (15.0%)	478 (29.0%)	91 (28.0%)	175 (42.1%)	126 (16.1%)
	21.8 (20.2,23.6)	16.3 (13.9,18.9)	20.4 (19.0,21.8)	23.2 (21.1,25.4)	33.7 (21.4,50.5)	23.5 (21.5,25.7)	31.4 (25.3,38.5)	49.1 (42.1,57.0)	41.7 (34.7,49.6)
TEAE with Grade 3 or Higher	260 (14.3%)	49 (10.9%)	309 (13.6%)	204 (13.7%)	2 (1.3%)	206 (12.5%)	29 (8.9%)	40 (9.6%)	44 (5.6%)
	8.7 (7.6,9.8)	4.7 (3.5,6.2)	7.6 (6.8,8.5)	10.4 (9.0,11.9)	2.9 (0.4,10.6)	10.1 (8.8,11.6)	10.0 (6.7,14.4)	11.2 (8.0,15.3)	14.6 (10.6,19.5)
TEAE Related to Study Drug with Grade 3 or Higher	107 (5.9%)	19 (4.2%)	126 (5.6%)	63 (4.2%)	1 (0.7%)	64 (3.9%)	13 (4.0%)	15 (3.6%)	16 (2.0%)
	3.6 (2.9,4.3)	1.8 (1.1,2.8)	3.1 (2.6,3.7)	3.2 (2.5,4.1)	1.5 (0.0,8.2)	3.1 (2.4,4.0)	4.5 (2.4,7.7)	4.2 (2.4,6.9)	5.3 (3.0,8.6)
TE Serious AE	198 (10.9%)	56 (12.4%)	254 (11.2%)	162 (10.8%)	4 (2.6%)	166 (10.1%)	22 (6.8%)	28 (6.7%)	31 (4.0%)
	6.6 (5.7,7.6)	5.4 (4.1,7.0)	6.3 (5.5,7.1)	8.2 (7.0,9.6)	5.9 (1.6,15.0)	8.2 (7.0,9.5)	7.6 (4.8,11.5)	7.9 (5.2,11.4)	10.3 (7.0,14.6)
TE Serious AE Related to Study Drug	69 (3.8%)	16 (3.6%)	85 (3.7%)	42 (2.8%)	1 (0.7%)	43 (2.6%)	10 (3.1%)	8 (1.9%)	5 (0.6%)
	2.3 (1.8,2.9)	1.5 (0.9,2.5)	2.1 (1.7,2.6)	2.1 (1.5,2.9)	1.5 (0.0,8.2)	2.1 (1.5,2.8)	3.4 (1.7,6.3)	2.2 (1.0,4.4)	1.7 (0.5,3.9)
TE Serious AE Leading to Death	14 (0.8%)	2 (0.4%)	16 (0.7%)	6 (0.4%)	0	6 (0.4%)	1 (0.3%)	0	1 (0.1%)
	0.5 (0.3,0.8)	0.2 (0.0,0.7)	0.4 (0.2,0.6)	0.3 (0.1,0.7)	0.0 (0.0,5.4)	0.3 (0.1,0.6)	0.3 (0.0,1.9)	0.0 (0.0,1.0)	0.3 (0.0,1.8)
TE Death	11 (0.6%)	1 (0.2%)	12 (0.5%)	6 (0.4%)	0	6 (0.4%)	1 (0.3%)	0	1 (0.1%)
	0.4 (0.2,0.7)	0.1 (0.0,0.5)	0.3 (0.2,0.5)	0.3 (0.1,0.7)	0.0 (0.0,5.4)	0.3 (0.1,0.6)	0.3 (0.0,1.9)	0.0 (0.0,1.0)	0.3 (0.0,1.8)
All Deaths	15 (0.8%)	4 (0.9%)	19 (0.8%)	6 (0.4%)	0	6 (0.4%)	1 (0.3%)	0	2 (0.3%)
	0.5 (0.3,0.8)	0.4 (0.1,1.0)	0.5 (0.3,0.7)	0.3 (0.1,0.7)	0.0 (0.0,5.4)	0.3 (0.1,0.6)	0.3 (0.0,1.9)	0.0 (0.0,1.0)	0.7 (0.1,2.4)
TEAE Leading to Premature Discontinuation of Study Drug	164 (9.0%)	76 (16.9%)	240 (10.6%)	85 (5.7%)	10 (6.5%)	95 (5.8%)	18 (5.5%)	25 (6.0%)	24 (3.1%)
	5.5 (4.7,6.4)	7.3 (5.7,9.1)	5.9 (5.2,6.7)	4.3 (3.5,5.3)	14.6 (7.0,26.9)	4.7 (3.8,5.7)	6.2 (3.7,9.8)	7.0 (4.5,10.4)	7.9 (5.1,11.8)
TEAE Leading to Temporary Interruption of Study Drug	492 (27.1%)	92 (20.4%)	584 (25.8%)	361 (24.2%)	6 (3.9%)	367 (22.3%)	45 (13.8%)	97 (23.3%)	72 (9.2%)
	16.4 (15.0,17.9)	8.8 (7.1,10.8)	14.4 (13.3,15.6)	18.4 (16.5,20.4)	8.8 (3.2,19.1)	18.1 (16.3,20.0)	15.5 (11.3,20.8)	27.2 (22.1,33.2)	23.8 (18.6,30.0)

AE = adverse event; csDMARD = conventional synthetic disease-modifying rheumatic drug; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily; TE = treatment emergent; TEAE = treatment-emergent adverse event
Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs).
Adverse events were coded according to MedDRA Version 22.0.
Severity grades were defined by or converted to the CTCAE Version 4.03.
Treatment-emergent events began on or after the first dose date of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo, and no later than the earlier date of either 30 days after the last dose date, or the first dose date of the switched treatment minus 1 day.
TEAEs leading to premature discontinuation or temporary interruption of study drug included subjects from GS-US-417-0303 that were discontinued or interrupted from MTX but continued filgotinib in filgotinib 200 mg once daily or filgotinib 100 mg once daily groups.
EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Adverse events of special interest

Adverse events of interest included

- Major adverse cardiovascular events (MACE)
- all infections
- serious infections
- infections of special interest (including herpes zoster, active TB, opportunistic infections, and hepatitis B or C infections)

- Deep venous thrombosis (DVT) and pulmonary embolism (PE)
- malignancy (including lymphoma; not including nonmelanoma skin cancer)
- nonmelanoma skin cancer, and
- gastrointestinal (GI) perforations.

MACE

Subjects at high risk for cardiovascular disease were excluded from the clinical studies, according to the following exclusion criterion (that was in place for all three phase 3 studies):

History of or current moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), or within the last 6 months, a cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia, new or significant ECG finding at screening, or any other cardiovascular condition which, in the opinion of the investigator, would have put the subject at risk by participation in the study.

Pooled data

Table 24 presents EAIRs of positively-adjudicated MACE for As Treated Subjects in the pooled safety population.

Table 24. Exposure-Adjusted Incidence Rates of Major Adverse Cardiovascular Events in the Pooled Safety Population (Safety Analysis Set, As Treated Subjects)

MACE Category	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)			
Major Adverse Cardiovascular Events (MACE)	13 (0.7%)	6 (1.3%)	19 (0.8%)	13 (0.9%)	0	13 (0.8%)	1 (0.3%)	2 (0.5%)	3 (0.4%)
	0.4 (0.2,0.7)	0.6 (0.2,1.3)	0.5 (0.3,0.7)	0.7 (0.4,1.1)	0.0 (0.0,5.4)	0.6 (0.3,1.1)	0.3 (0.0,1.9)	0.6 (0.1,2.0)	1.0 (0.2,2.9)
Cardiovascular Death	5 (0.3%)	1 (0.2%)	6 (0.3%)	4 (0.3%)	0	4 (0.2%)	0	0	0
	0.2 (0.1,0.4)	0.1 (0.0,0.5)	0.1 (0.1,0.3)	0.2 (0.1,0.5)	0.0 (0.0,5.4)	0.2 (0.1,0.5)	0.0 (0.0,1.3)	0.0 (0.0,1.0)	0.0 (0.0,1.2)
Non-Fatal Myocardial Infarction	2 (0.1%)	2 (0.4%)	4 (0.2%)	5 (0.3%)	0	5 (0.3%)	1 (0.3%)	0	2 (0.3%)
	0.1 (0.0,0.2)	0.2 (0.0,0.7)	0.1 (0.0,0.3)	0.3 (0.1,0.6)	0.0 (0.0,5.4)	0.2 (0.1,0.6)	0.3 (0.0,1.9)	0.0 (0.0,1.0)	0.7 (0.1,2.4)
Non-Fatal Stroke	7 (0.4%)	3 (0.7%)	10 (0.4%)	4 (0.3%)	0	4 (0.2%)	0	2 (0.5%)	1 (0.1%)
	0.2 (0.1,0.5)	0.3 (0.1,0.8)	0.2 (0.1,0.5)	0.2 (0.1,0.5)	0.0 (0.0,5.4)	0.2 (0.1,0.5)	0.0 (0.0,1.3)	0.6 (0.1,2.0)	0.3 (0.0,1.8)

CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs). Multiple AEs were counted only once per subject for each treatment period for each preferred term. Preferred terms were presented by descending order of total frequencies.

MACE were assessed by an independent cardiovascular safety endpoint adjudication committee. Only the adjudicated positive MACE were included.

Adverse events were coded according to MedDRA Version 22.0.

EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Infections

Exposure-adjusted incidence rates of infectious AEs for As Treated Subjects in the pooled safety population is presented in the *Table 25*. *Table 26* presents EAIRs of infectious AEs reported for at least 3% of As Treated Subjects in any treatment group by PT in the pooled safety population.
Exposure-adjusted incidence rates of serious infectious AEs for As Treated Subjects in the pooled safety population is presented in *Table 27*.

Table 25. Exposure-Adjusted Incidence Rates of Infectious AEs in the Pooled Safety Population by (Safety Analysis Set, As Treated Subjects)

Treatment-Emergent Adverse Event of Interest	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)			
Infectious Adverse Event	864 (47.6%)	210 (46.7%)	1074 (47.4%)	623 (41.7%)	25 (16.3%)	648 (39.3%)	129 (39.7%)	157 (37.7%)	167 (21.4%)
	28.8 (26.9,30.8)	20.1 (17.5,23.0)	26.5 (25.0,28.2)	31.7 (29.3,34.3)	36.6 (23.7,54.1)	31.9 (29.5,34.4)	44.5 (37.1,52.8)	44.1 (37.5,51.5)	55.2 (47.2,64.3)

CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; MACE = major adverse cardiovascular events; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs).

Only the adjudicated positive MACE were included.

AEs of special interest are identified by either lab results, standardized MedDRA queries, or sponsor-defined medical search terms, or a combination of these methods.

Adverse events were coded according to MedDRA Version 22.0.

EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Table 26. Exposure-Adjusted Incidence Rates of All Infectious AEs Reported for At Least 3% of Subjects in Any Treatment Group in the Pooled Safety Population by Preferred Term (Safety Analysis Set, As Treated Subjects)

Preferred Term	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)			
Number (%) of Subjects with Any Treatment-Emergent Infectious Adverse Event	864 (47.6%)	210 (46.7%)	1074 (47.4%)	623 (41.7%)	25 (16.3%)	648 (39.3%)	129 (39.7%)	157 (37.7%)	167 (21.4%)
Upper respiratory tract infection	176 (9.7%)	48 (10.7%)	224 (9.9%)	122 (8.2%)	5 (3.3%)	127 (7.7%)	21 (6.5%)	34 (8.2%)	23 (2.9%)
	5.9 (5.0,6.8)	4.6 (3.4,6.1)	5.5 (4.8,6.3)	6.2 (5.2,7.4)	7.3 (2.4,17.1)	6.2 (5.2,7.4)	7.2 (4.5,11.1)	9.5 (6.6,13.3)	7.6 (4.8,11.4)
Nasopharyngitis	171 (9.4%)	41 (9.1%)	212 (9.4%)	134 (9.0%)	1 (0.7%)	135 (8.2%)	24 (7.4%)	25 (6.0%)	36 (4.6%)
	5.7 (4.9,6.6)	3.9 (2.8,5.3)	5.2 (4.6,6.0)	6.8 (5.7,8.1)	1.5 (0.0,8.2)	6.6 (5.6,7.9)	8.3 (5.3,12.3)	7.0 (4.5,10.4)	11.9 (8.3,16.5)
Urinary tract infection	130 (7.2%)	34 (7.6%)	164 (7.2%)	90 (6.0%)	7 (4.6%)	97 (5.9%)	17 (5.2%)	11 (2.6%)	12 (1.5%)
	4.3 (3.6,5.1)	3.3 (2.3,4.5)	4.1 (3.5,4.7)	4.6 (3.7,5.6)	10.3 (4.1,21.1)	4.8 (3.9,5.8)	5.9 (3.4,9.4)	3.1 (1.5,5.5)	4.0 (2.1,6.9)
Bronchitis	109 (6.0%)	23 (5.1%)	132 (5.8%)	67 (4.5%)	2 (1.3%)	69 (4.2%)	10 (3.1%)	16 (3.8%)	24 (3.1%)
	3.6 (3.0,4.4)	2.2 (1.4,3.3)	3.3 (2.7,3.9)	3.4 (2.6,4.3)	2.9 (0.4,10.6)	3.4 (2.6,4.3)	3.4 (1.7,6.3)	4.5 (2.6,7.3)	7.9 (5.1,11.8)
Influenza	62 (3.4%)	12 (2.7%)	74 (3.3%)	37 (2.5%)	2 (1.3%)	39 (2.4%)	6 (1.8%)	9 (2.2%)	12 (1.5%)
	2.1 (1.6,2.6)	1.1 (0.6,2.0)	1.8 (1.4,2.3)	1.9 (1.3,2.6)	2.9 (0.4,10.6)	1.9 (1.4,2.6)	2.1 (0.8,4.5)	2.5 (1.2,4.8)	4.0 (2.1,6.9)
Pharyngitis	55 (3.0%)	17 (3.8%)	72 (3.2%)	27 (1.8%)	1 (0.7%)	28 (1.7%)	6 (1.8%)	8 (1.9%)	13 (1.7%)
	1.8 (1.4,2.4)	1.6 (0.9,2.6)	1.8 (1.4,2.2)	1.4 (0.9,2.0)	1.5 (0.0,8.2)	1.4 (0.9,2.0)	2.1 (0.8,4.5)	2.2 (1.0,4.4)	4.3 (2.3,7.4)
Latent tuberculosis	48 (2.6%)	14 (3.1%)	62 (2.7%)	40 (2.7%)	2 (1.3%)	42 (2.6%)	0	0	0
	1.6 (1.2,2.1)	1.3 (0.7,2.2)	1.5 (1.2,2.0)	2.0 (1.5,2.8)	2.9 (0.4,10.6)	2.1 (1.5,2.8)	0.0 (0.0,1.3)	0.0 (0.0,1.0)	0.0 (0.0,1.2)
Herpes zoster	54 (3.0%)	18 (4.0%)	72 (3.2%)	23 (1.5%)	0	23 (1.4%)	2 (0.6%)	4 (1.0%)	3 (0.4%)

Preferred Term	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab	MTX	Placebo
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)	+ MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	(N=781) (PYE=302.4) n (%) EAIR (95% CI)
	1.8 (1.4,2.3)	1.7 (1.0,2.7)	1.8 (1.4,2.2)	1.2 (0.7,1.8)	0.0 (0.0,5.4)	1.1 (0.7,1.7)	0.7 (0.1,2.5)	1.1 (0.3,2.9)	1.0 (0.2,2.9)

CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs).

Multiple AEs were counted only once per subject for each treatment period for each preferred term. Preferred terms were presented by descending order of total frequencies.

Infectious adverse events were defined as all preferred terms in the infections and infestations system organ class.

Adverse events were coded according to MedDRA Version 22.0.

EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Table 27. Exposure-Adjusted Incidence Rates of Serious Infectious AEs in the Pooled Safety Population (Safety Analysis Set, As Treated Subjects)

Treatment-Emergent Adverse Event of Interest	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)			
Serious Infectious Adverse Event	48 (2.6%)	19 (4.2%)	67 (3.0%)	48 (3.2%)	3 (2.0%)	51 (3.1%)	10 (3.1%)	8 (1.9%)	7 (0.9%)
	1.6 (1.2,2.1)	1.8 (1.1,2.8)	1.7 (1.3,2.1)	2.4 (1.8,3.2)	4.4 (0.9,12.8)	2.5 (1.9,3.3)	3.4 (1.7,6.3)	2.2 (1.0,4.4)	2.3 (0.9,4.8)

CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs).

Adverse events of special interest are identified by either lab results, standardized MedDRA queries, or sponsor-defined medical search terms, or a combination of these methods.

Adverse events were coded according to MedDRA Version 22.0.

EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Infections of special interest

Herpes zoster

Exposure-adjusted incidence rates for As Treated Subjects in the pooled safety population is presented in *Table 28*.

Table 28. Exposure-Adjusted Incidence Rates of Herpes Zoster Adverse Events in the Pooled Safety Population (Safety Analysis Set, As Treated Subjects)

Treatment-Emergent Adverse Event of Interest	Filgotinib 200 mg QD + csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Filgotinib 200 mg QD Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Filgotinib 200 mg QD Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	Filgotinib 100 mg QD + csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Filgotinib 100 mg QD Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Filgotinib 100 mg QD Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)	Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
Herpes Zoster	56 (3.1%)	18 (4.0%)	74 (3.3%)	23 (1.5%)	0	23 (1.4%)	2 (0.6%)	4 (1.0%)	3 (0.4%)
	1.9 (1.4,2.4)	1.7 (1.0,2.7)	1.8 (1.4,2.3)	1.2 (0.7,1.8)	0.0 (0.0,5.4)	1.1 (0.7,1.7)	0.7 (0.1,2.5)	1.1 (0.3,2.9)	1.0 (0.2,2.9)

CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs). Adverse events of special interest are identified by either lab results, standardized MedDRA queries, or sponsor-defined medical search terms, or a combination of these methods. Adverse events were coded according to MedDRA Version 22.0.

EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Active tuberculosis

No AEs of active tuberculosis (TB) reported during the first 12 weeks of treatment for As Randomized Subjects. A total of 4 subjects in the pooled safety population had AEs of active TB. Of these, 3 subjects were in the filgotinib 100 mg + MTX group in LTE Study GS-US-417-0304, and 1 subject was in the adalimumab + MTX group in Study GS-US-417-0301.

Opportunistic infections (including tuberculosis)

During the first 12 weeks of treatment for As Randomized Subjects, no subject in the filgotinib or other treatment groups, and 1 subject (0.3%) in the adalimumab group had an opportunistic infection AE.

Exposure-adjusted incidence rates of opportunistic infections for As Treated Subjects in the pooled safety population is shown in *Table 29*.

Table 29. Exposure-Adjusted Incidence Rates of Opportunistic Infections Including Tuberculosis in the Pooled Safety Population (Safety Analysis Set, As Treated Subjects)

Treatment-Emergent Adverse Event of Interest	Filgotinib 200 mg QD + csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Filgotinib 200 mg QD Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Filgotinib 200 mg QD Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	Filgotinib 100 mg QD + csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Filgotinib 100 mg QD Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Filgotinib 100 mg QD Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)	Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
Opportunistic Infections	4 (0.2%)	1 (0.2%)	5 (0.2%)	4 (0.3%)	0	4 (0.2%)	2 (0.6%)	2 (0.5%)	0
	0.1	0.1	0.1	0.2	0.0	0.2	0.7	0.6	0.0

	(0.0,0.3)	(0.0,0.5)	(0.0,0.3)	(0.1,0.5)	(0.0,5.4)	(0.1,0.5)	(0.1,2.5)	(0.1,2.0)	(0.0,1.2)

CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs). Adverse events of special interest are identified by either lab results, standardized MedDRA queries, or sponsor-defined medical search terms, or a combination of these methods. Adverse events were coded according to MedDRA Version 22.0.

EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Hepatitis B or C infections

In phase 2 studies, subjects with positive serology for hepatitis B or C were excluded from participation. In phase 3 studies, subjects with evidence of prior exposure to hepatitis B (Hep B core antibody positive, surface antigen negative and Hep B DNA negative) and/or hepatitis C (Hep C antibody positive) were allowed to enrol. They were monitored every 3 months by hepatitis B DNA or hepatitis C RNA testing.

Adverse events of Hepatitis B or C infections reported during the first 12 weeks of treatment for As Randomized Subjects were reported for 1 subject (<0.1%) in the filgotinib 200 mg group/total filgotinib group (Hepatitis B DNA assay positive). No subject in the filgotinib 100 mg, adalimumab, or other groups had an AE of hepatitis B or C infection.

The frequency of hepatitis B-related AEs for As Treated Subjects in the Phase 3 studies (up to week 52) was as follows: filgotinib 200 mg: 0.4%; filgotinib 100 mg: 0.4%; adalimumab: 0.3%.

Deep vein thrombosis (DVT) and pulmonary embolism (PE)

Table 30 presents EAIRs of positively-adjudicated VTE for As Treated Subjects in the pooled safety population.

Table 30. Exposure-Adjusted Incidence Rates of Positively Adjudicated Venous Thrombotic and Embolic Events in the Pooled Safety Population (Safety Analysis Set, As Treated Subjects)

Venous Thromboembolism (VTE)	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)			
Venous Thromboembolism (VTE): DVT/PE	8 (0.4%)	0	8 (0.4%)	1 (<0.1%)	0	1 (<0.1%)	1 (0.3%)	2 (0.5%)	2 (0.3%)
	0.3 (0.1,0.5)	0.0 (0.0,0.4)	0.2 (0.1,0.4)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)	0.3 (0.0,1.9)	0.6 (0.1,2.0)	0.7 (0.1,2.4)
Deep Vein Thrombosis (DVT)	6 (0.3%)	0	6 (0.3%)	0	0	0	1 (0.3%)	0	2 (0.3%)
	0.2 (0.1,0.4)	0.0 (0.0,0.4)	0.1 (0.1,0.3)	0.0 (0.0,0.2)	0.0 (0.0,5.4)	0.0 (0.0,0.2)	0.3 (0.0,1.9)	0.0 (0.0,1.0)	0.7 (0.1,2.4)
Pulmonary Embolism (PE)	6 (0.3%)	0	6 (0.3%)	1 (<0.1%)	0	1 (<0.1%)	0	2 (0.5%)	0
	0.2 (0.1,0.4)	0.0 (0.0,0.4)	0.1 (0.1,0.3)	0.1 (0.0,0.3)	0.0 (0.0,5.4)	0.0 (0.0,0.3)	0.0 (0.0,1.3)	0.6 (0.1,2.0)	0.0 (0.0,1.2)

CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs).

Multiple AEs were counted only once per subject for each treatment period for each preferred term. Preferred terms were presented by descending order of total frequencies.

Adverse events of special interest are identified by either lab results, standardized MedDRA queries, or sponsor-defined medical search terms, or a combination of these methods.

Adverse events were coded according to MedDRA Version 22.0.

EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Malignancies

All cancers excluding non-melanoma skin cancers (NMSC)

Exposure-adjusted incidence rates of all malignancies excluding NMSC for As Treated Subjects in the pooled safety population is presented in *Table 31*.

Non-melanoma skin cancer

Exposure-adjusted incidence rates of NMSCs for As Treated Subjects in the pooled safety population is presented in *Table 32*.

Table 31. Exposure-Adjusted Incidence Rates of Malignancies Excluding Nonmelanoma Skin Cancer in the Pooled Safety Population (Safety Analysis Set, As Treated Subjects)

Treatment-Emergent Adverse Event of Interest	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)			
Malignancy Excluding Nonmelanoma Skin Cancer	18 (1.0%)	4 (0.9%)	22 (1.0%)	11 (0.7%)	0	11 (0.7%)	2 (0.6%)	4 (1.0%)	3 (0.4%)
	0.6 (0.4,0.9)	0.4 (0.1,1.0)	0.5 (0.3,0.8)	0.6 (0.3,1.0)	0.0 (0.0,5.4)	0.5 (0.3,1.0)	0.7 (0.1,2.5)	1.1 (0.3,2.9)	1.0 (0.2,2.9)

CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs). Adverse events of special interest are identified by either lab results, standardized MedDRA queries, or sponsor-defined medical search terms, or a combination of these methods. Adverse events were coded according to MedDRA Version 22.0.

EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Table 32. Exposure-Adjusted Incidence Rates of Nonmelanoma Skin Cancer in the Pooled Safety Population (Safety Analysis Set, As Treated Subjects)

Treatment-Emergent Adverse Event of Interest	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)			
Nonmelanoma Skin Cancer	8 (0.4%)	1 (0.2%)	9 (0.4%)	3 (0.2%)	0	3 (0.2%)	0	1 (0.2%)	0
	0.3 (0.1,0.5)	0.1 (0.0,0.5)	0.2 (0.1,0.4)	0.2 (0.0,0.4)	0.0 (0.0,5.4)	0.1 (0.0,0.4)	0.0 (0.0,1.3)	0.3 (0.0,1.6)	0.0 (0.0,1.2)

CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs). Adverse events of special interest are identified by either lab results, standardized MedDRA queries, or sponsor-defined medical search terms, or a combination of these methods. Adverse events were coded according to MedDRA Version 22.0.

EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Gastrointestinal perforations

Overall, 3 GI perforations were observed in As Treated Subjects in the pooled safety population. All of these subjects were in the filgotinib 200 mg + csDMARDs group.

Serious adverse event/deaths/other significant events

Deaths

Pooled data

Table 33 presents EAIRs of all deaths in the full Safety Analysis Set for As Treated Subjects in the pooled safety population.

Table 33. Exposure-Adjusted Incidence Rates of All Deaths in the Pooled Safety Population (Safety Analysis Set, As Treated Subjects)

All Deaths	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX	MTX Monotherapy	Placebo
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)	(N=325) (PYE=290.1) n (%) EAIR (95% CI)	(N=416) (PYE=356.2) n (%) EAIR (95% CI)	(N=781) (PYE=302.4) n (%) EAIR (95% CI)
Death	15 (0.83%)	4 (0.89%)	19 (0.84%)	6 (0.40%)	0	6 (0.36%)	1 (0.31%)	0	2 (0.26%)
	0.5 (0.3,0.8)	0.4 (0.1,1.0)	0.5 (0.3,0.7)	0.3 (0.1,0.7)	0.0 (0.0,5.4)	0.3 (0.1,0.6)	0.3 (0.0,1.9)	0.0 (0.0,1.0)	0.7 (0.1,2.4)

CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily
Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs).
EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Table 34 presents a summary of all deaths reported through the data cutoff dates. Newly reported deaths since the time of the original submission are bolded in the table below. Deaths that occurred for subjects in the filgotinib 100 mg twice daily treatment group in Studies GLPG0634-CL-203 and GLPG0634-CL-205 were not included in the EAIR calculation for once-daily dosing but are discussed below. Deaths that were reported after 3 subjects discontinued from study were also not included in the EAIR calculation and are also discussed below.

Table 34. All Deaths in the Pooled Phase 2 and Phase 3 Safety Population

Study	Treatment Group	Day of Last Dose of Study Drug[a]	Day of Death[a]	Cause of Death[b]
Deaths due to Cardiovascular Disease				
GLPG0634-CL-205	Filgotinib 100 mg BID	915[c]	919[c]	Pulmonary embolism and deep vein thrombosis (positively adjudicated as CV death)
GS-US-417-0301	Placebo to Filgotinib 200 mg QD	205	224	Acute deep vein thrombosis (positively adjudicated as CV death)
GS-US-417-0303	Filgotinib 200 mg QD	211[d]	279	Unknown – likely cardiac related (positively adjudicated as CV death)
GS-US-417-0303	Filgotinib 200 mg QD	7	7	Lupus myocardiopathy (positively adjudicated as CV death)
GS-US-417-0304	Filgotinib 200 mg QD	258	268	Initial: ischemic stroke; secondary: sepsis; direct: heart failure (positively adjudicated as CV death)
GS-US-417-0304	Filgotinib 200 mg QD	104	104	Exudative pericarditis with thrombosis of inferior vena cava and left brachiocephalic vein (positively adjudicated as CV death)
GS-US-417-0304	Filgotinib 200 mg QD	7	Not available	Stroke (positively adjudicated as CV death)
GS-US-417-0301	Filgotinib 100 mg QD	13	14	Myocardial infarction (positively adjudicated as CV death)
GS-US-417-0303	Filgotinib 100 mg QD	306	318	Subarachnoid hemorrhage of the left middle cerebral artery (positively adjudicated as CV death)
GS-US-417-0304	Filgotinib 100 mg QD	132	132	Cardiac arrest (positively adjudicated as CV death)
GS-US-417-0304	Filgotinib 100 mg QD	92	117	Cardiorespiratory failure (unable to adjudicate)
GS-US-417-0304	**Filgotinib 200 mg QD**	**499**	**499**	**Acute myocardial infarction (positively adjudicated as CV death)**

Study	Treatment Group	Day of Last Dose of Study Drug[a]	Day of Death[a]	Cause of Death[b]
Deaths due to Infections				
GLPG0634-CL-205	Filgotinib 200 mg QD	586[c]	588[c]	Pneumonia
GS-US-417-0301	Filgotinib 200 mg QD	25	30	Septic shock secondary to multisegmental pneumonia
GS-US-417-0301	Filgotinib 200 mg QD	110	123	Septic shock
GS-US-417-0304	Filgotinib 200 mg QD	186	189	Refractory septic shock
GLPG0634-CL-203	Filgotinib 100 mg BID	83	105	Pneumonia and septic shock
GLPG0634-CL-205	Filgotinib 100 mg BID	496[c]	507[c]	Meningococcal meningitis
GS-US-417-0301	Adalimumab	271	284	Sepsis
GS-US-417-0301	Placebo to Filgotinib 100 mg QD	360	368	Varicella
GS-US-417-0301	Placebo	27	84	Septic shock
GS-US-417-0304	**Filgotinib 200 mg QD**	**422**	**468**	**Worsening of *Staphylococcus aureus* sepsis and severe dysphagia[e]**
Deaths due to Malignancies				
GLPG0634-CL-205	Filgotinib 200 mg QD	Unspecified; between 736 and 765[c]	790[c]	Non-Hodgkin's lymphoma
GLPG0634-CL-205	Filgotinib 200 mg QD	260[c]	626[c]	Non-Hodgkin's lymphoma
GS-US-417-0304	Filgotinib 200 mg QD	237	237	Metastatic adenocarcinoma of the lung
GLPG0634-CL-205	**Filgotinib 100 mg BID**	**1395[c]**	**1406[c]**	**Metastatic leiomyosarcoma of cutaneous origin**
GS-US-417-0304	**Filgotinib 200 mg QD**	**223**	**237**	**Heart failure due to pericardial effusion due to neoplasm[f]**
GS-US-417-0304	**Filgotinib 200 mg QD**	**545**	**637**	**Squamous cell carcinoma of the esophagus**
GS-US-417-0304	**Filgotinib 100 mg QD**	**214**	**241**	**Acute left ventricular failure due to malignant peritoneal neoplasm and ovarian cancer[g]**
Deaths due to Other Reasons				
GS-US-417-0301	Filgotinib 200 mg QD	182	234	Alveolitis
GS-US-417-0303	Filgotinib 200 mg QD	266	274	Atypical interstitial pneumonia
GS-US-417-0301	Placebo	8	14	Toxicity to various agents
Additional Deaths after the Subject had Left the Study				
GLPG0634-CL-205	**Filgotinib 200 mg QD**	**930**	**~6 months after last dose**	**"Death" (see further information below)**
GS-US-417-0301	**Placebo**	**28**	**~18 months after study discontinuation**	**Fatal malignant glioma (see further information below)**
GS-US-417-0303	**MTX**	**191**	**~18 months after study discontinuation**	**Small cell lung cancer (see further information below)**

BID = twice daily; CV = cardiovascular; CVEAC = cardiovascular safety endpoint adjudication committee; ID = identification; MACE = major adverse cardiac event; MTX = methotrexate; QD = once daily; SAE = serious adverse event

a Day relative to date of first dose of any study drug in a study

b All deaths were adjudicated for MACE by an independent CVEAC.

c For indicated subjects from Study GLPG0634-CL-205, the day of last dose of study drug and day of death are based on information provided in subject narratives of deaths (GLPG0634-CL-205 Interim 1 Amendment, Narratives)

d Last dose of study drug imputed based on Days to Death After Last Dose = 68

e The death for one Subject has not yet been adjudicated by the CVEAC.

f The Grade 5 SAE of cardiac failure for one Subject was negatively adjudicated as MACE by the CVEAC.

g The Grade 5 SAE of malignant peritoneal neoplasm for one Subject was negatively adjudicated as MACE by the CVEAC.

Data from separate phase 3 studies – FINCH1

Data from FINCH1 that includes adalimumab as an active comparator is shown in *Table 35*. FINCH 1 was a MTX add-on study.

Table 35. GS-US-417-0301: Overall Summary of Adverse Events (Safety Analysis Set)

Active-Controlled Period (Overall Period)						
				Placebo[a]		
Number (%) of Subjects with Any	Filgotinib 200 mg (N=475)	Filgotinib 100 mg (N=480)	Adalimumab (N=325)	On Filgotinib 200 mg Period (N=190)	On Filgotinib 100 mg Period (N=191)	On Placebo Period (N=475)
TEAE	352 (74.1%)	350 (72.9%)	239 (73.5%)	92 (48.4%)	97 (50.8%)	254 (53.5%)
TEAE with Grade 3 or Higher	58 (12.2%)	54 (11.3%)	29 (8.9%)	14 (7.4%)	11 (5.8%)	33 (6.9%)
TEAE Related to Study Drug	148 (31.2%)	137 (28.5%)	91 (28.0%)	21 (11.1%)	29 (15.2%)	87 (18.3%)
TEAE Related to Study Drug with Grade 3 or Higher	31 (6.5%)	19 (4.0%)	13 (4.0%)	4 (2.1%)	3 (1.6%)	12 (2.5%)
TE Serious AE	35 (7.4%)	40 (8.3%)	22 (6.8%)	7 (3.7%)	8 (4.2%)	21 (4.4%)
TE Serious AE Related to Study Drug	17 (3.6%)	12 (2.5%)	10 (3.1%)	1 (0.5%)	2 (1.0%)	5 (1.1%)
TEAE Leading to Premature Discontinuation of Any Study Drug	26 (5.5%)	15 (3.1%)	18 (5.5%)	6 (3.2%)	2 (1.0%)	15 (3.2%)
TEAE Leading to Premature Discontinuation of Study	17 (3.6%)	8 (1.7%)	8 (2.5%)	2 (1.1%)	1 (0.5%)	10 (2.1%)
TEAE Leading to Temporary Interruption of Any Study Drug	83 (17.5%)	90 (18.8%)	45 (13.8%)	17 (8.9%)	21 (11.0%)	47 (9.9%)
Death	3 (0.6%)	1 (0.2%)	1 (0.3%)	1 (0.5%)	1 (0.5%)	2 (0.4%)
TE Serious AE Leading to Death	3 (0.6%)	1 (0.2%)	1 (0.3%)	1 (0.5%)	1 (0.5%)	1 (0.2%)

AE = adverse event; TE = treatment emergent; TEAE = treatment-emergent adverse event
a At Week 24, subjects in the placebo group who did not discontinue placebo were rerandomized to filgotinib 200 mg or 100 mg. These groups are referred to as the placebo to filgotinib 200 mg group and the placebo to filgotinib 100 mg group. All placebo group exposure is limited to approximately 24 weeks.
Safety Analysis Set includes subjects who received at least 1 dose of study drug. Adverse events were coded with MedDRA Version 22.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
For rerandomized subjects, TEAEs started prior to the first dose date of filgotinib were allocated to the placebo-controlled period, and TEAEs started on or after the first dose date of filgotinib were allocated to the rerandomized period.
Severity grades were defined by the CTCAE Version 4.03. Death includes any death that occurred during the study.

Serious adverse events

Table 36 presents an overall summary of SAEs for As Treated Subjects in the pooled safety population.

Table 36 Overall Summary of Serious Adverse Events in the Pooled Safety Population (Safety Analysis Set, As Treated Subjects)

Number (%) of Subjects with Any	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)			
TE Serious AE	198 (10.9%)	56 (12.4%)	254 (11.2%)	162 (10.8%)	4 (2.6%)	166 (10.1%)	22 (6.8%)	28 (6.7%)	31 (4.0%)
	6.6 (5.7,7.6)	5.4 (4.1,7.0)	6.3 (5.5,7.1)	8.2 (7.0,9.6)	5.9 (1.6,15.0)	8.2 (7.0,9.5)	7.6 (4.8,11.5)	7.9 (5.2,11.4)	10.3 (7.0,14.6)

Pneumonia was the most common treatment-emergent SAE reported across all treatment groups for As Treated Subjects (filgotinib 200 mg: 13 subjects, 0.6%, filgotinib 100 mg: 7 subjects, 0.4%; adalimumab: 2 subjects, 0.6%; MTX monotherapy: 1 subject, 0.2%). Rheumatoid arthritis (worsening) was the most commonly reported SAE in the other treatment group (3 subjects, 0.3%).

The exposure-adjusted incidence rate for SAEs of pneumonia was 0.4 per 100 PYE in the filgotinib 200 mg group, 0.5 per 100 PYE in the filgotinib 100 mg group, 0.7 per 100 PYE in the adalimumab group, and 0.8 per 100 PYE in the MTX monotherapy group.

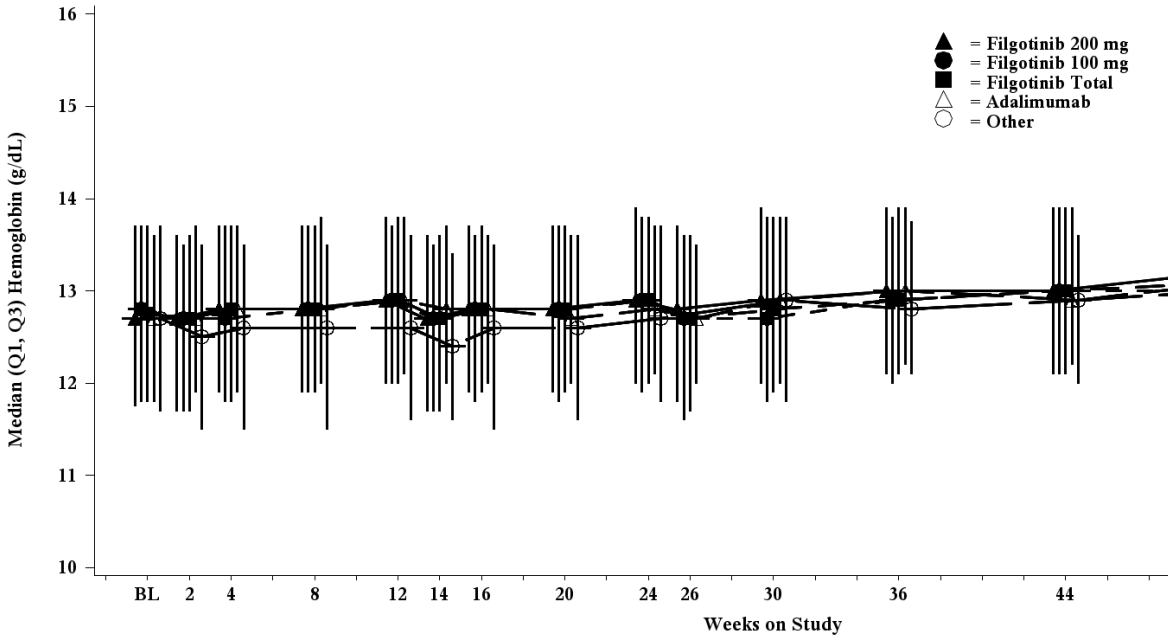
Laboratory findings

According to the applicant, the clinical laboratory safety profile in the Phase 1 and Phase 2 studies indicated that filgotinib was generally well tolerated.

Haematology parameters

Haemoglobin

Median (first quartile [Q1], third quartile [Q3]) haemoglobin values (g/dL) by visit for As Randomized Subjects in the Pooled Phase 3 Parent Studies (GS-US-417-0301, GS-US-417-0302, and GS-US-417-0303) are shown in Figure 7.



Filgotinib 200 mg (n=):	1248	1210	1218	1195	1170	566	1136	1123	1092	412	787	629	448
Filgotinib 100 mg (n=):	840	821	802	809	777	577	756	746	726	409	546	443	301
Filgotinib Total (n=):	2088	2031	2020	2004	1947	1143	1892	1869	1818	821	1333	1072	749
Adalimumab (n=):	325	314	316	315	306	293	287	289	283	280	265	208	145
Other (n=):	1039	1010	992	978	941	526	875	852	830		250	196	143

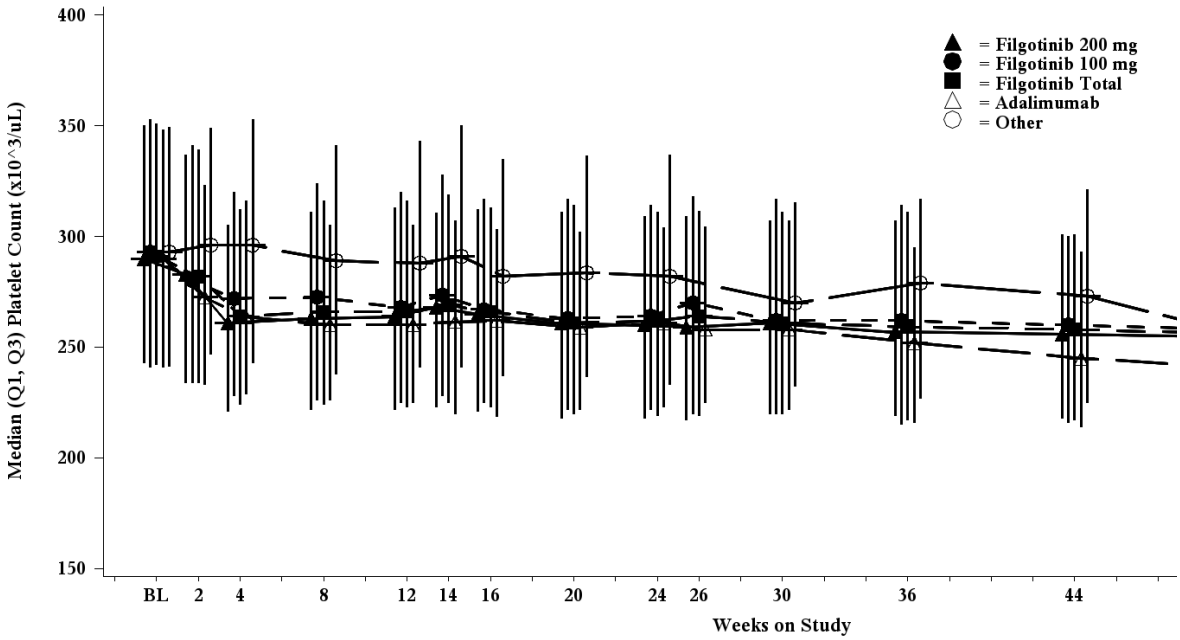
BL = Baseline

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, or other (Placebo ± MTX or csDMARDs, and MTX monotherapy). Baseline value was the last available value collected on or prior to first dose of any study drug in the parent study.

Figure 7 Median (Q1, Q3) Hemoglobin (g/dL) by Visit in Studies GS-US-417-0301, GS-US-417-0302, and GS US 417 0303 (As Randomized Subjects, Safety Analysis Set)

Platelets

According to the applicant, a slight decrease in median platelet count values was initially seen in the filgotinib treatment groups and the adalimumab group. These decreases stabilized by Week 4, and median (Q1, Q3) platelet values in all treatment groups were within the normal laboratory reference range over time.



Filgotinib 200 mg (n=):	1247	1196	1204	1183	1161	564	1126	1111	1080	409	783	625	445
Filgotinib 100 mg (n=):	840	817	797	802	773	574	751	739	717	407	543	439	298
Filgotinib Total (n=):	2087	2013	2001	1985	1934	1138	1877	1850	1797	816	1326	1064	743
Adalimumab (n=):	325	312	314	311	300	290	284	286	277	276	263	205	143
Other (n=):	1036	1003	983	973	932	523	865	844	818		248	195	142

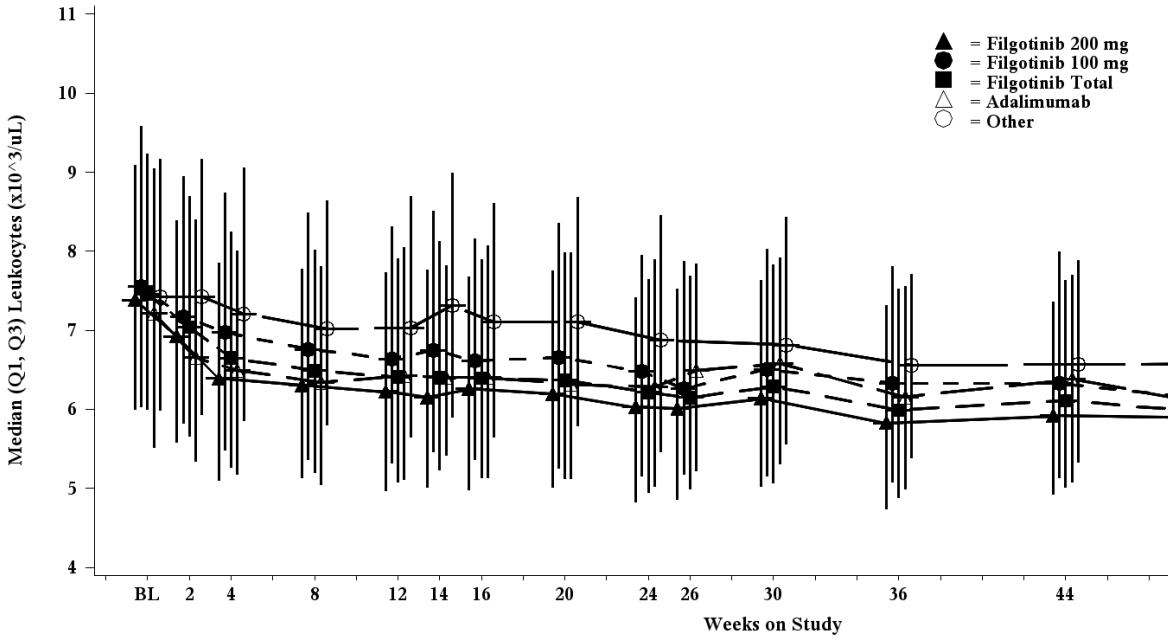
BL = Baseline

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, or other (Placebo ± MTX or csDMARDs, and MTX monotherapy). Baseline value was the last available value collected on or prior to first dose of any study drug in the parent study.

Figure 8 Median (Q1, Q3) Platelet Count (x10^3/µL) by Visit in Studies GS-US-417-0301, GS-US-417-0302, and GS US 417 0303 (As Randomized Subjects, Safety Analysis Set up to Week 24)

Leukocytes

Median (Q1, Q3) leukocyte values (× 10^3/µL) by visit for As Randomized Subjects in the Pooled Phase 3 Parent Studies (GS-US-417-0301, GS-US-417-0302, and GS-US-417-0303) are shown in the Figure 9.



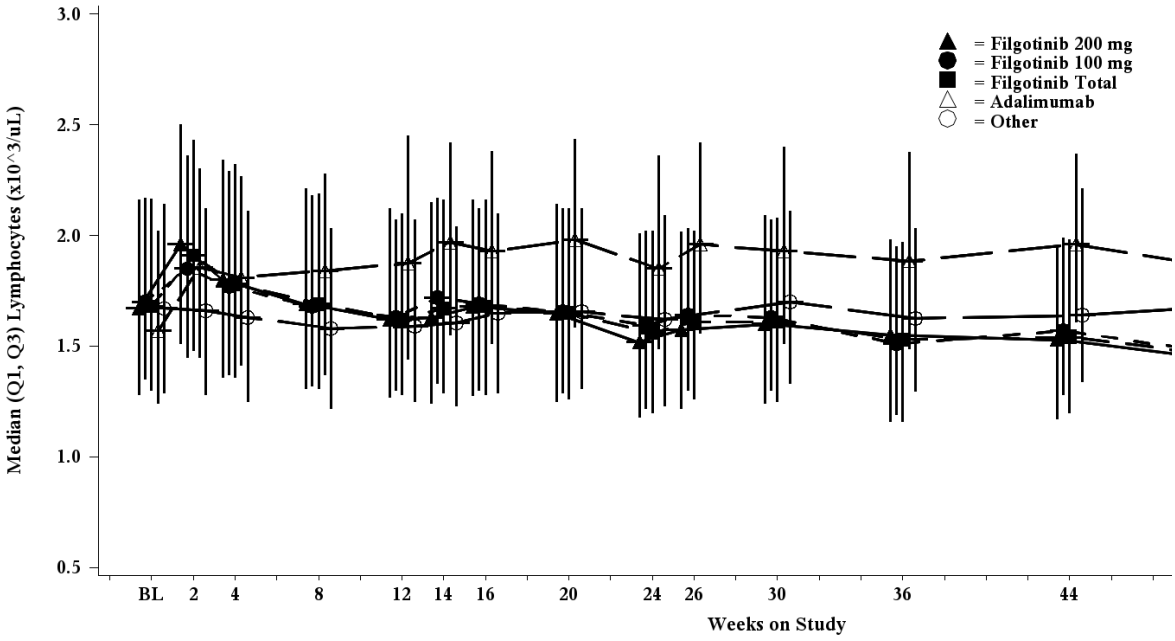
Filgotinib 200 mg (n=):	1248	1210	1218	1195	1170	566	1136	1123	1092	412	787	629	448
Filgotinib 100 mg (n=):	840	821	802	809	777	577	756	746	726	409	546	443	301
Filgotinib Total (n=):	2088	2031	2020	2004	1947	1143	1892	1869	1818	821	1333	1072	749
Adalimumab (n=):	325	314	316	315	306	293	287	289	283	280	265	208	145
Other (n=):	1039	1010	992	978	941	526	875	852	830		250	196	143

BL = Baseline

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, or other (Placebo ± MTX or csDMARDs, and MTX monotherapy). Baseline value was the last available value collected on or prior to first dose of any study drug in the parent study.

Figure 9 Median (Q1, Q3) Leukocytes (x10^3/µL) by Visit in Studies GS-US-417-0301, GS-US-417-0302, and GS US 417 0303 (As Randomized Subjects, Safety Analysis Set)

Lymphocytes



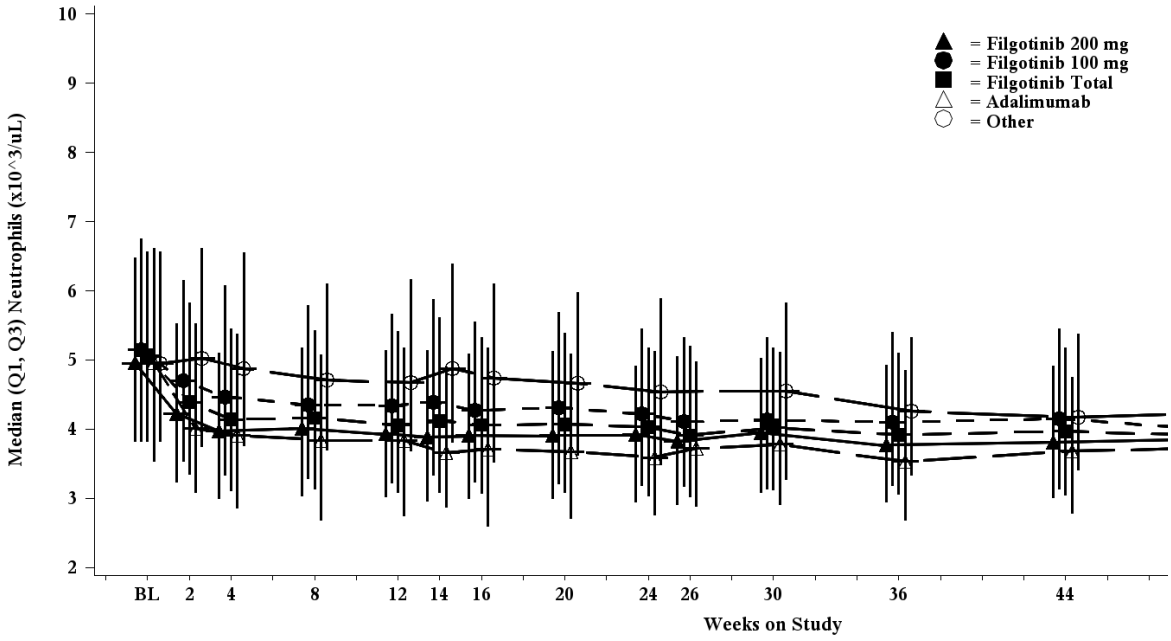
Filgotinib 200 mg (n=):	1248	1210	1215	1194	1170	566	1136	1123	1091	412	787	629	448
Filgotinib 100 mg (n=):	840	821	802	808	776	577	755	746	726	409	546	443	301
Filgotinib Total (n=):	2088	2031	2017	2002	1946	1143	1891	1869	1817	821	1333	1072	749
Adalimumab (n=):	325	314	316	315	306	293	286	288	283	279	265	208	145
Other (n=):	1039	1008	992	978	941	526	875	850	829		250	196	143

BL = Baseline

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, or other (Placebo ± MTX or csDMARDs, and MTX monotherapy). Baseline value was the last available value collected on or prior to first dose of any study drug in the parent study.

Figure 10 Median (Q1, Q3) Lymphocytes (x10^3/µL) by Visit in Studies GS-US-417-0301, GS-US-417-0302, and GS US 417 0303 (As Randomized Subjects, Safety Analysis Set)

Neutrophils



Filgotinib 200 mg (n=):	1248	1210	1215	1194	1170	566	1136	1123	1091	412	787	629	448
Filgotinib 100 mg (n=):	840	821	802	808	776	577	755	746	726	409	546	443	301
Filgotinib Total (n=):	2088	2031	2017	2002	1946	1143	1891	1869	1817	821	1333	1072	749
Adalimumab (n=):	325	314	316	315	306	293	286	288	283	279	265	208	145
Other (n=):	1039	1008	992	978	941	526	875	850	829		250	196	143

BL = Baseline

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, or other (Placebo ± MTX or csDMARDs, and MTX monotherapy). Baseline value was the last available value collected on or prior to first dose of any study drug in the parent study.

Figure 11 Median (Q1, Q3) Neutrophils (x10^3/µL) by Visit in Studies GS-US-417-0301, GS-US-417-0302, and GS US 417 0303 (As Randomized Subjects, Safety Analysis Set)

Lipid parameters

Deranges in lipid parameters are shown in Figure 12 and Figure 13.

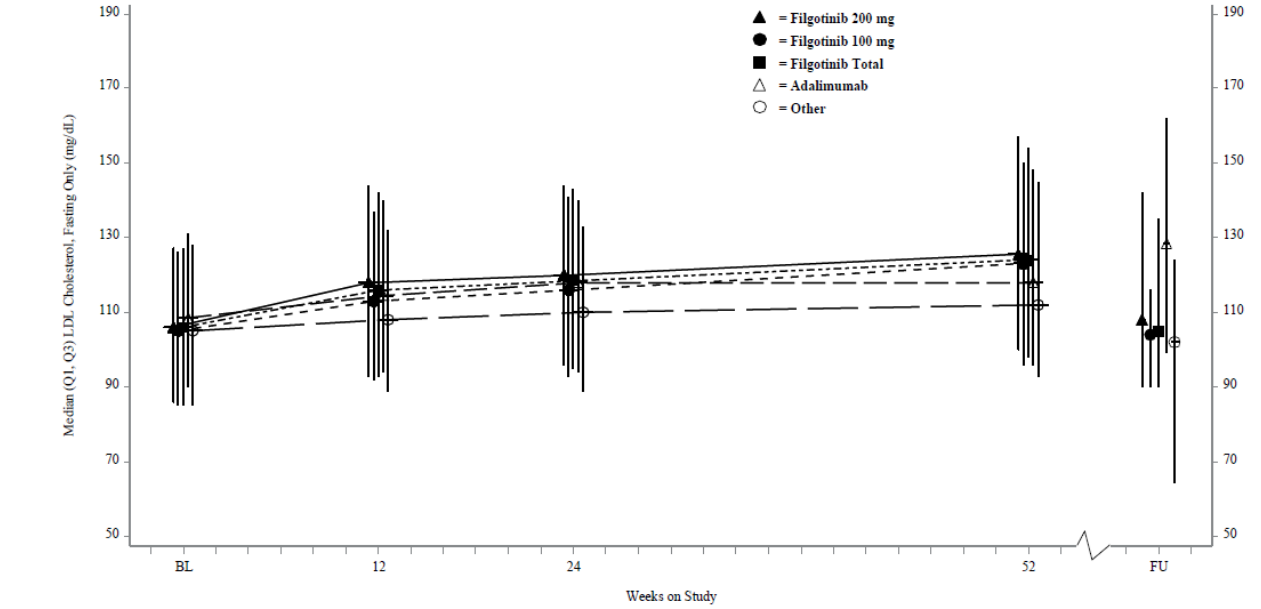


Figure 12 Median (Q1, Q3) Chemistry: LDL Cholesterol (mg/dL) and Change from Baseline - Fasting Only, Safety Analysis Set, As Randomized Subjects (GS-US-417-0301, GS-US-417-0302 and GS-US-17-0303)

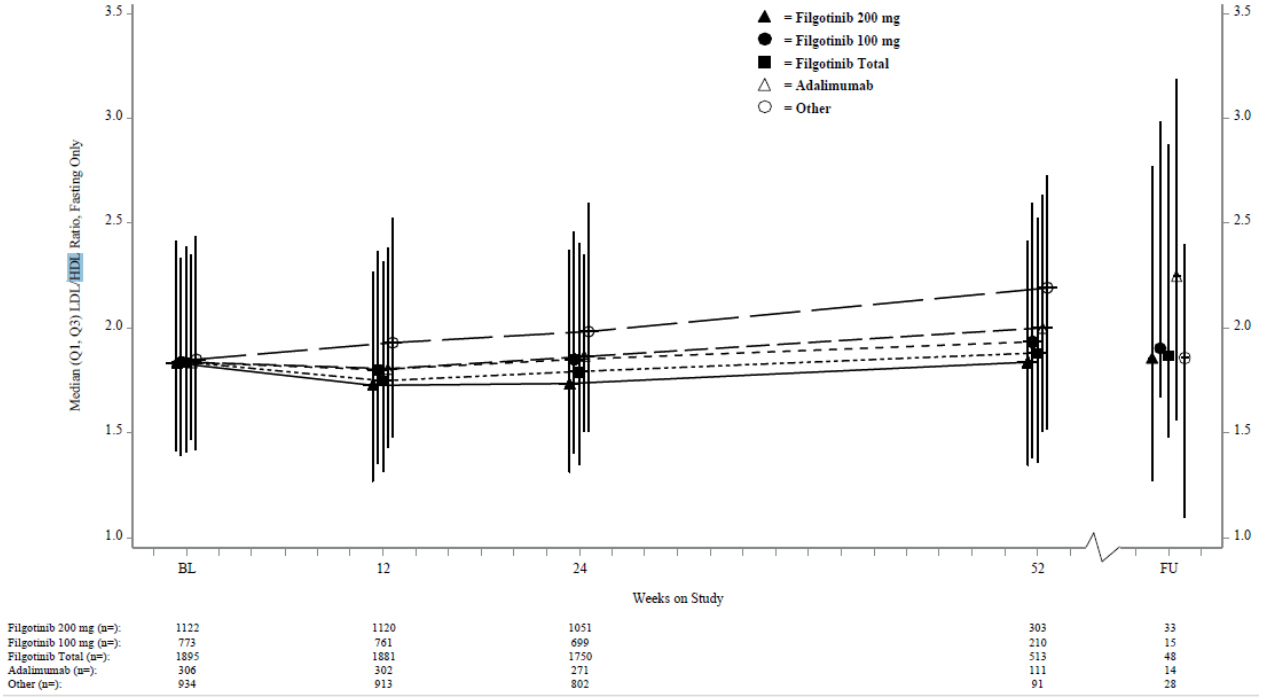
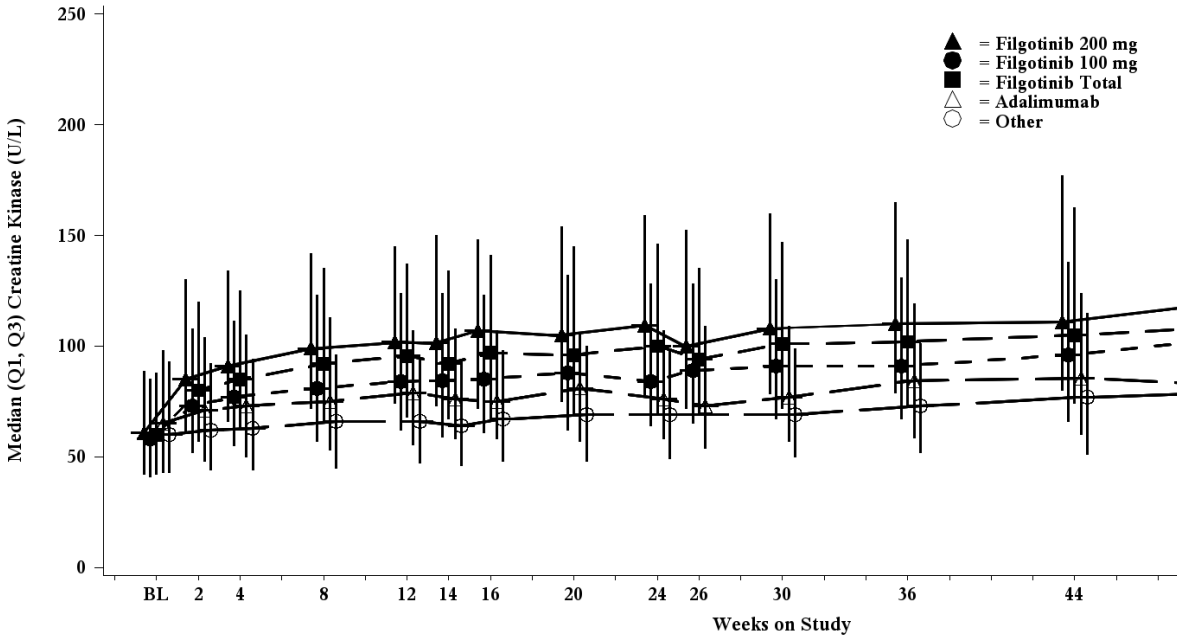


Figure 13 Median (Q1, Q3) Chemistry: LDL/HDL Ratio by Visit - Fasting Only, Safety Analysis Set, As Randomized Subjects (GS-US-417-0301, GS-US-417-0302 and GS-US-417-0303)

Chemistry parameters

Creatine kinase



Filgotinib 200 mg (n=):	1248	1220	1228	1200	1177	570	1147	1127	1098	412	792	633	449
Filgotinib 100 mg (n=):	839	827	816	815	789	580	762	748	729	409	547	446	303
Filgotinib Total (n=):	2087	2047	2044	2015	1966	1150	1909	1875	1827	821	1339	1079	752
Adalimumab (n=):	325	318	319	319	308	294	291	288	285	279	267	208	146
Other (n=):	1039	1019	1001	986	952	527	880	855	836		252	199	143

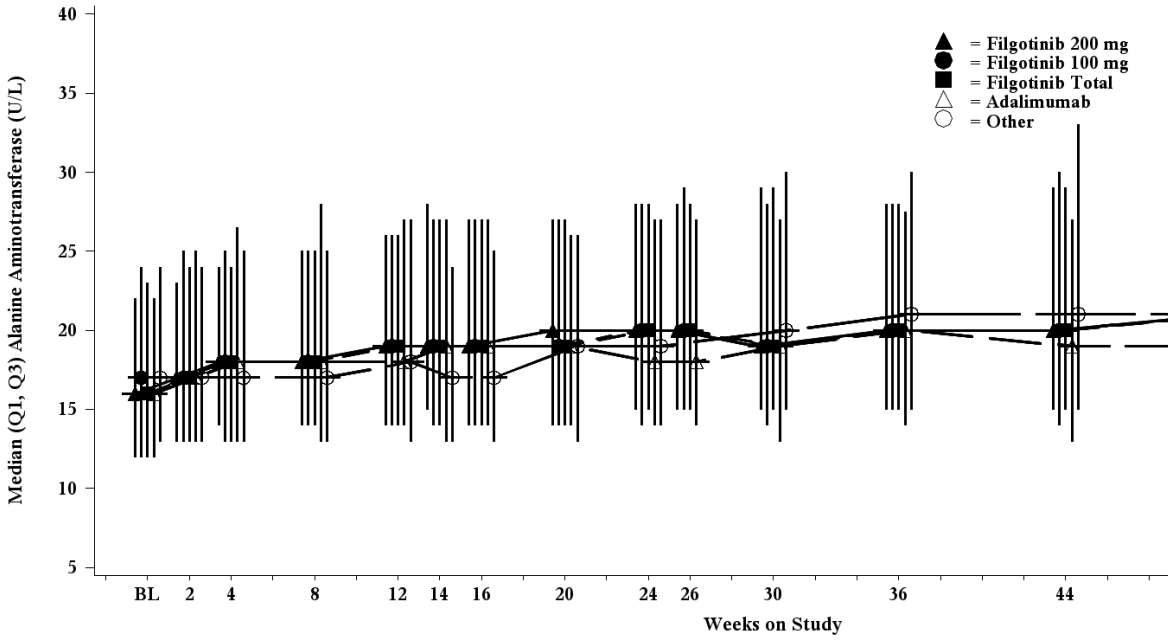
BL = Baseline

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, or other (Placebo ± MTX or csDMARDs, and MTX monotherapy). Baseline value was the last available value collected on or prior to first dose of any study drug in the parent study.

Figure 14 Median (Q1, Q3) Creatine Kinase (U/L) by Visit in Studies GS-US-417-0301, GS-US-417-0302, and GS US 417 0303 (As Randomized Subjects, Safety Analysis Set)

Liver-related parameters

Deranges in liver parameters up to current data cut-off in the phase 3 studies are shown in Figure 15 and Figure 16.

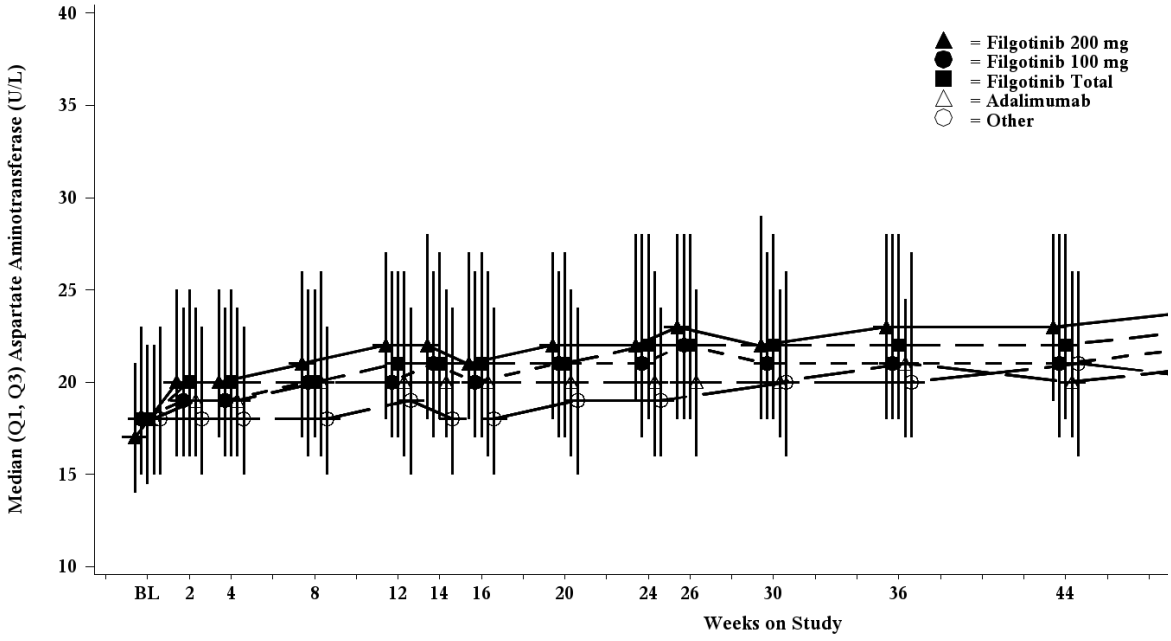


Filgotinib 200 mg (n=):	1248	1220	1228	1200	1178	570	1147	1126	1097	412	792	633	449
Filgotinib 100 mg (n=):	840	827	816	815	789	580	762	748	729	409	547	446	303
Filgotinib Total (n=):	2088	2047	2044	2015	1967	1150	1909	1874	1826	821	1339	1079	752
Adalimumab (n=):	325	318	320	319	308	294	291	288	285	279	267	208	146
Other (n=):	1039	1020	1001	985	952	527	879	855	835		252	199	143

BL = Baseline

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, or other (Placebo ± MTX or csDMARDs, and MTX monotherapy). Baseline value was the last available value collected on or prior to first dose of any study drug in the parent study.

Figure 15 Median (Q1, Q3) Alanine Aminotransferase (U/L) by Visit in Studies GS-US-417-0301, GS-US-417-0302, and GS US 417 0303 (As Randomized Subjects, Safety Analysis Set)



Filgotinib 200 mg (n=):	1248	1217	1225	1199	1174	569	1145	1124	1094	410	791	632	447
Filgotinib 100 mg (n=):	840	825	814	813	786	576	760	743	727	409	543	445	303
Filgotinib Total (n=):	2088	2042	2039	2012	1960	1145	1905	1867	1821	819	1334	1077	750
Adalimumab (n=):	323	315	319	319	308	293	291	287	284	277	267	208	146
Other (n=):	1039	1014	1000	983	950	526	876	853	834		252	198	143

BL = Baseline

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, or other (Placebo ± MTX or csDMARDs, and MTX monotherapy). Baseline value was the last available value collected on or prior to first dose of any study drug in the parent study.

Figure 16 Median (Q1, Q3) Aspartate Aminotransferase (U/L) by Visit in Studies GS-US-417-0301, GS US 417 0302, and GS US 417 0303 (As Randomized Subjects, Safety Analysis Set)

Comparative data between filgotinib in monotherapy and filgotinib in combination with csDMARDs from FINCH 3 is shown in *Table 37*.

Table 37. FINCH3: Grade 3 or Higher Laboratory Abnormalities, Up to the Data Cutoff Date (Safety Analysis Set)

Maximum Postbaseline Toxicity Grade	Filgotinib 200 mg + MTX (N=416)	Filgotinib 100 mg + MTX (N=207)	Filgotinib 200 mg Monotherapy (N=210)	MTX Monotherapy (N=416)
Chemistry				
Alanine Aminotransferase (Increased)	413	204	207	413
Grade 3 or 4	15 (3.6%)	5 (2.5%)	1 (0.5%)	2 (0.5%)
Grade 3	15 (3.6%)	5 (2.5%)	1 (0.5%)	2 (0.5%)
Aspartate Aminotransferase (Increased)	413	204	207	413
Grade 3 or 4	5 (1.2%)	3 (1.5%)	2 (1.0%)	0
Grade 3	5 (1.2%)	3 (1.5%)	2 (1.0%)	0

Other findings relevant to safety

Vital signs and body weight

According to the applicant, there were no clinically relevant changes in any treatment group or differences between treatment groups in mean values for systolic blood pressure, diastolic blood pressure, pulse, respiration rate, or body temperature in the Phase 3 study population.

According to the applicant, in the Phase 1 Safety Populations, no safety signals for vital signs or physical findings were identified.

ECG findings

A thorough QT study (GS-US-417-3911) was performed. According to the ICH guideline, a negative thorough QT/QTc study is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms. For filgotinib, at all time-points, the upper bound of the 95% one-sided confidence interval is below 10 ms, and the criterion has thus been fulfilled.

ECG findings in phase 2 and 3 studies

In Study GLPG0634-CL-204, 1 subject in the placebo group had an abnormal ECG shift that was reported as an AE and led to study drug discontinuation. No additional clinically relevant shifts in ECG parameters were reported for subjects in the Phase 2 and Phase 1 Safety Populations.

Safety in special populations

Age

Pooled Phase 2 and Phase 3 Safety Population < 65 and ≥ 65 Years of Age, As Treated Subjects

A tabular summary of the frequency and EAIRs of treatment-emergent AEs (TEAEs), SAEs, and AEIs for As Treated Subjects in the pooled Phase 2 and Phase 3 safety studies by age group is presented in Table *Table 38*, *Table 39*, *Table 40* and *Table 41*.

Table 38. Overall Summary of Treatment-Emergent Adverse Events by Age Group (< 65, ≥ 65 years) (Safety Analysis Set, As Treated Subjects)

	< 65 Years of Age					≥ 65 Years of Age				
N (%) Subjects EAIR (95% CI)	Filgotinib 200 mg ± csDMARDs (N=2267) PYE=4047.7	Filgotinib 100 mg ± csDMARDs (N=1647) PYE=2032.9	Adalimumab + MTX (N=325) PYE=290.1	MTX Monotherapy (N=416) PYE=356.2	Placebo (N=781) PYE=302.4	Filgotinib 200 mg ± csDMARDs (N=2267) PYE=4047.7	Filgotinib 100 mg ± csDMARDs (N=1647) PYE=2032.9	Adalimumab+ MTX (N=325) PYE=290.1	MTX Monotherapy (N=416) PYE=356.2	Placebo (N=781) PYE=302.4
	n = 1857	n = 1320	n = 258	n = 329	n = 623	n = 410	n = 327	n = 67	n = 87	n = 158
TEAE	1430 (77.0%) 42.2 (40.0,44.4)	907 (68.7%) 56.3 (52.7,60.1)	186 (72.1%) 80.2 (69.1,92.6)	241 (73.3%) 86.3 (75.8,98.0)	328 (52.6%) 135.4 (121.1,150.9)	341 (83.2%) 52.0 (46.6,57.8)	233 (71.3%) 55.1 (48.3,62.7)	53 (79.1%) 91.0 (68.2,119.1)	64 (73.6%) 83.0 (64.0,106.0)	98 (62.0%) 163.0 (132.4,198.7)
TE Serious AE	171 (9.2%) 5.0 (4.3,5.9)	124 (9.4%) 7.7 (6.4,9.2)	15 (5.8%) 6.5 (3.6,10.7)	19 (5.8%) 6.8(4.1,10.6)	24 (3.9%) 9.9 (6.3,14.7)	83 (20.2%) 12.6 (10.1,15.7)	42 (12.8%) 9.9 (7.2,13.4)	7 (10.4%) 12.0 (4.8,24.8)	9 (10.3%) 11.7(5.3,22.2)	7 (4.4%) 11.6 (4.7,24.0)
Infectious AE	861 (46.4%) 25.4 (23.7,27.1)	519 (39.3%) 32.2 (29.5,35.1)	100 (38.8%) 43.1 (35.1,52.5)	126 (38.3%) 45.1 (37.6,53.8)	131 (21.0%) 54.1 (45.2,64.2)	213 (52.0%) 32.5 (28.2,37.1)	129 (39.4%) 30.5 (25.5,36.3)	29 (43.3%) 49.8 (33.4,71.5)	31 (35.6%) 40.2 (27.3,57.1)	36 (22.8%) 59.9 (41.9,82.9)
Serious Infectious AE	50 (2.7%) 1.5 (1.1,1.9)	40 (3.0%) 2.5 (1.8,3.4)	6 (2.3%) 2.6 (0.9,5.6)	6 (1.8%) 2.1 (0.8,4.7)	4 (0.6%) 1.7 (0.4,4.2)	17 (4.1%) 2.6 (1.5,4.1)	11 (3.4%) 2.6 (1.3,4.7)	4 (6.0%) 6.9 (1.9,17.6)	2 (2.3%) 2.6 (0.3,9.4)	3 (1.9%) 5.0 (1.0,14.6)

Table 39. Overall Summary of Treatment-Emergent Adverse Events by Age Group (< 75, ≥ 75 years) (Safety Analysis Set, As Treated Subjects)

	< 75 Years of Age					≥ 75 Years of Age				
N (%) Subjects EAIR (95% CI)	Filgotinib 200 mg ± csDMARDs (N=2267) PYE=4047.7	Filgotinib 100 mg ± csDMARDs (N=1647) PYE=2032.9	Adalimumab + MTX (N=325) PYE=290.1	MTX Monotherapy (N=416) PYE=356.2	Placebo (N=781) PYE=302.4	Filgotinib 200 mg ± csDMARDs (N=2267) PYE=4047.7	Filgotinib 100 mg ± csDMARDs (N=1647) PYE=2032.9	Adalimumab+ MTX (N=325) PYE=290.1	MTX Monotherapy (N=416) PYE=356.2	Placebo (N=781) PYE=302.4
	n = 2191	n = 1580	n = 311	n = 400	n = 756	n = 76	n = 67	n = 14	n = 16	n = 25
TEAE	1703 (77.7%) 43.4 (41.3,45.5)	1097 (69.4%) 56.2 (52.9,59.7)	226 (72.7%) 81.7 (71.4,93.1)	296 (74.0%) 86.7 (77.1,97.2)	413 (54.6%) 141.3 (128.0,155.6)	68 (89.5%) 56.7 (44.1,71.9)	43 (64.2%) 52.5 (38.0,70.7)	13 (92.9%) 95.8 (51.0,163.8)	9 (56.3%) 61.0 (27.9,115.8)	13 (52.0%) 128.5 (68.4,219.7)
TE Serious AE	230 (10.5%) 5.9 (5.1,6.7)	156 (9.9%) 8.0 (6.8,9.4)	21 (6.8%) 7.6 (4.7,11.6)	27 (6.8%) 7.9 (5.2,11.5)	29 (3.8%) 9.9 (6.6,14.3)	24 (31.6%) 20.0 (12.8,29.8)	10 (14.9%) 12.2 (5.9,22.4)	1 (7.1%) 7.4 (0.2,41.0)	1 (6.3%) 6.8 (0.2,37.8)	2 (8.0%) 19.8 (2.4,71.4)
Infectious AE	1033 (47.1%) 26.3 (24.7,28.0)	622 (39.4%) 31.9 (29.4,34.5)	120 (38.6%) 43.4 (36.0,51.9)	152 (38.0%) 44.5 (37.7,52.2)	165 (21.8%) 56.5 (48.2,65.8)	41 (53.9%) 34.2 (24.6,46.4)	26 (38.8%) 31.7 (20.7,46.5)	9 (64.3%) 66.3 (30.3,125.9)	5 (31.3%) 33.9 (11.0,79.1)	2 (8.0%) 19.8 (2.4,71.4)
Serious Infectious AE	62 (2.8%) 1.6 (1.2,2.0)	48 (3.0%) 2.5 (1.8,3.3)	10 (3.2%) 3.6 (1.7,6.7)	8 (2.0%) 2.3 (1.0,4.6)	7 (0.9%) 2.4 (1.0,4.9)	5 (6.6%) 4.2 (1.4,9.7)	3 (4.5%) 3.7 (0.8,10.7)	0 0.0 (0.0,27.2)	0 0.0 (0.0,25.0)	0 0.0 (0.0,36.5)

Table 40. Safety Profile by Age Groups - Filgotinib 200 mg Once Daily (Pooled Safety Population, As Treated Subjects)

Number (%) of Subjects with Any Treatment-Emergent	Age in Years			
	< 65 (N = 1857)	65-74 (N = 334)	75-84 (N = 75)	≥ 85 (N = 1)
Total AEs	1430 (77.0%)	273 (81.7%)	68 (90.7%)	0
Serious AEs – Total	171 (9.2%)	59 (17.7%)	24 (32.0%)	0
Fatal	9 (0.5%)	6 (1.8%)	1 (1.3%)	0
Hospitalization/Prolonged Existing Hospitalization	151 (8.1%)	53 (15.9%)	22 (29.3%)	0
Life-threatening	39 (2.1%)	9 (2.7%)	5 (6.7%)	0
Disability/Incapacity	1 (< 0.1%)	0	1 (1.3%)	0
Other (medically significant)	11 (0.6%)	7 (2.1%)	2 (2.7%)	0
AE Leading to Discontinuation of Study Drug	177 (9.5%)	47 (14.1%)	16 (21.3%)	0
Psychiatric Disorders	77 (4.1%)	13 (3.9%)	5 (6.7%)	0
Nervous System Disorders	219 (11.8%)	53 (15.9%)	12 (16.0%)	0
Accidents and Injuries	168 (9.0%)	53 (15.9%)	15 (20.0%)	0
Cardiac Disorders	68 (3.7%)	25 (7.5%)	9 (12.0%)	0
Vascular Disorders	144 (7.8%)	39 (11.7%)	10 (13.3%)	0
Cerebrovascular Disorders	10 (0.5%)	9 (2.7%)	2 (2.7%)	0
Infections and Infestations	861 (46.4%)	172 (51.5%)	41 (54.7%)	0
Anticholinergic Syndrome	0	0	0	0
Quality of Life Decreased	0	0	0	0
Sum of Postural Hypotension, Falls, Black-outs, Syncope, Dizziness, Ataxia, Fractures	114 (6.1%)	38 (11.4%)	14 (18.7%)	0
Dizziness	37 (2.0%)	11 (3.3%)	4 (5.3%)	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events
As Treated Subjects includes subjects who received at least 1 dose of study drug of interest in the individual study.
Treatment-emergent AEs were included. Adverse events were coded according to MedDRA Version 22.0.
Severity grades were defined by or converted to the CTCAE Version 4.03.
"Life-threatening" refers to CTCAE Grade 4.
"Disability/incapacity" and "Other (medically significant)" were collected from FINCH 1, FINCH 2, FINCH 3, and FINCH 4

Table 41. Safety Profile by Age Groups - Filgotinib 100 mg Once Daily (Pooled Safety Population, As Treated Subjects)

Number (%) of Subjects with Any Treatment-Emergent	Age in Years			
	< 65 (N = 1320)	65-74 (N = 260)	75-84 (N = 66)	≥ 85 (N = 1)
Total AEs	907 (68.7%)	190 (73.1%)	42 (63.6%)	1 (100.0%)
Serious AEs – Total	124 (9.4%)	32 (12.3%)	10 (15.2%)	0
Fatal	5 (0.4%)	1 (0.4%)	0	0
Hospitalization/Prolonged Existing Hospitalization	111 (8.4%)	31 (11.9%)	9 (13.6%)	0
Life-threatening	14 (1.1%)	4 (1.5%)	1 (1.5%)	0
Disability/Incapacity	2 (0.2%)	0	0	0
Other (medically significant)	9 (0.7%)	4 (1.5%)	1 (1.5%)	0
AE Leading to Discontinuation of Study Drug	71 (5.4%)	21 (8.1%)	3 (4.5%)	0
Psychiatric Disorders	53 (4.0%)	11 (4.2%)	1 (1.5%)	0
Nervous System Disorders	128 (9.7%)	35 (13.5%)	8 (12.1%)	0
Accidents and Injuries	102 (7.7%)	29 (11.2%)	4 (6.1%)	1 (100.0%)
Cardiac Disorders	39 (3.0%)	13 (5.0%)	3 (4.5%)	0
Vascular Disorders	81 (6.1%)	15 (5.8%)	5 (7.6%)	0
Cerebrovascular Disorders	8 (0.6%)	5 (1.9%)	3 (4.5%)	0
Infections and Infestations	519 (39.3%)	103 (39.6%)	25 (37.9%)	1 (100.0%)
Anticholinergic Syndrome	0	0	0	0
Quality of Life Decreased	0	0	0	0
Sum of Postural Hypotension, Falls, Black-outs, Syncope, Dizziness, Ataxia, Fractures	63 (4.8%)	23 (8.8%)	4 (6.1%)	1 (100.0%)
Dizziness	16 (1.2%)	8 (3.1%)	1 (1.5%)	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events
As Treated Subjects includes subjects who received at least 1 dose of study drug of interest in the individual study.
Treatment-emergent AEs were included. Adverse events were coded according to MedDRA Version 22.0.
Severity grades were defined by or converted to the CTCAE Version 4.03.
"Life-threatening" refers to CTCAE Grade 4.
"Disability/incapacity" and "Other (medically significant)" were collected from FINCH 1, FINCH 2, FINCH 3, and FINCH 4

Sex

According to the applicant, the percentage of As Treated Subjects in the Pooled Phase 2 and Phase 3 Safety Studies who experienced any AE, any SAE or any serious infection was similar for male subjects and female subjects across all treatment groups.

Hepatic impairment

A total of 10 subjects with moderate hepatic impairment (Child-Turcotte-Pugh [CPT] B) and 10 healthy matched control subjects received a single, oral dose of filgotinib 100 mg in Study GS-US-417-4048. No deaths, SAEs, or discontinuations due to AEs were reported. Three subjects (30.0%) with moderate

hepatic impairment and 1 healthy matched control subject (10.0%) experienced AEs. All AEs were Grade 1 in severity. Filgotinib was, according to the applicant, generally well tolerated in subjects with moderate hepatic impairment and normal hepatic function.

The applicant stated that because exposures of filgotinib and its primary metabolite GS-829845 were not significantly impacted by moderate hepatic impairment, filgotinib and GS-829845 PK was not evaluated in subjects with mild hepatic impairment. The applicant further stated that no dose adjustment is necessary in subjects with mild or moderate hepatic impairment but as filgotinib has not been evaluated in subjects with severe hepatic impairment it is not recommended for use in this patient population.

Renal impairment

A total of 6 subjects with mild renal impairment, 6 subjects with moderate renal impairment, 3 subjects with severe renal impairment, and 9 subjects with normal renal function received filgotinib 100 mg once daily for 10 days in Study GLPG0634-CL-106.

No deaths, SAEs, or discontinuations due to AEs were reported among these subjects. Three subjects (33.3%) with normal renal function, 1 subject (16.7%) with mild renal impairment, and 1 subject (16.7%) with moderate renal impairment experienced AEs. All AEs were mild or moderate in severity. According to the applicant, there were no clinically significant safety-related changes on laboratory parameters.

Furthermore, according to the applicant, mild renal impairment had no impact on filgotinib or GS-829845 PK when compared to subjects with normal renal function. Moderate and severe renal impairment modestly increased filgotinib exposure (AUCtau) by 1.5-fold. In subjects with severe renal impairment the recommended dose of filgotinib is 100 mg once daily. No dose adjustment is recommended in subjects with mild renal impairment. In response to day 180 LoQ, the applicant presented safety data in patients with moderate renal impairment (GFR 30-60, *Table 42*).

Table 42. EAIR of TEAEs: Overall Summary for Subjects with Moderate Renal Impairment at Baseline Estimated Glomerular Filtration Rate (Safety Analysis Set, As Treated Subjects)

	Filgotinib 200 mg QD			Filgotinib 100 mg QD		
Number (%) of Subjects with Any	**+ csDMARDs (N=1817) PYE=3003.3 n (%) EAIR (95% CI)**	**Monotherapy (N=450) PYE=1044.4 n (%) EAIR (95% CI)**	**Total (N=2267) PYE=4047.7 n (%) EAIR (95% CI)**	**+ csDMARDs (N=1494) PYE=1964.7 n (%) EAIR (95% CI)**	**Monotherapy (N=153) PYE=68.3 n (%) EAIR (95% CI)**	**Total (N=1647) PYE=2032.9 n (%) EAIR (95% CI)**
eGFR at Baseline: 30 <= eGFR <60 mL/min/1.73 m^2	77	20	97	55	3	58
TEAE	62 (80.5%) 58.5 (44.8,75.0)	17 (85.0%) 48.7 (28.4,78.0)	79 (81.4%) 56.1 (44.4,69.9)	36 (65.5%) 50.8 (35.6,70.3)	1 (33.3%) 143.8 (3.6,801.2)	37 (63.8%) 51.7 (36.4,71.2)
TEAE Related to Study Drug	29 (37.7%) 27.4 (18.3,39.3)	7 (35.0%) 20.1 (8.1,41.3)	36 (37.1%) 25.6 (17.9,35.4)	9 (16.4%) 12.7 (5.8,24.1)	0 0.0 (0.0,530.5)	9 (15.5%) 12.6 (5.7,23.9)
TEAE with Grade 3 or Higher	19 (24.7%) 17.9 (10.8,28.0)	3 (15.0%) 8.6 (1.8,25.1)	22 (22.7%) 15.6 (9.8,23.6)	8 (14.5%) 11.3 (4.9,22.2)	0 0.0 (0.0,530.5)	8 (13.8%) 11.2 (4.8,22.0)
TEAE Related to Study Drug with Grade 3 or Higher	9 (11.7%) 8.5 (3.9,16.1)	1 (5.0%) 2.9 (0.1,16.0)	10 (10.3%) 7.1 (3.4,13.1)	0 0.0 (0.0,5.2)	0 0.0 (0.0,530.5)	0 0.0 (0.0,5.2)
TE Serious AE	16 (20.8%) 15.1 (8.6,24.5)	4 (20.0%) 11.5 (3.1,29.4)	20 (20.6%) 14.2 (8.7,21.9)	6 (10.9%) 8.5 (3.1,18.4)	0 0.0 (0.0,530.5)	6 (10.3%) 8.4 (3.1,18.2)
TE Serious AE Related to Study Drug	8 (10.4%) 7.5 (3.3,14.9)	1 (5.0%) 2.9 (0.1,16.0)	9 (9.3%) 6.4 (2.9,12.1)	0 0.0 (0.0,5.2)	0 0.0 (0.0,530.5)	0 0.0 (0.0,5.2)

Number (%) of Subjects with Any	Filgotinib 200 mg QD			Filgotinib 100 mg QD		
	+ csDMARDs (N=1817) PYE=3003.3 n (%) EAIR (95% CI)	Monotherapy (N=450) PYE=1044.4 n (%) EAIR (95% CI)	Total (N=2267) PYE=4047.7 n (%) EAIR (95% CI)	+ csDMARDs (N=1494) PYE=1964.7 n (%) EAIR (95% CI)	Monotherapy (N=153) PYE=68.3 n (%) EAIR (95% CI)	Total (N=1647) PYE=2032.9 n (%) EAIR (95% CI)
TE Serious AE Leading to Death	2 (2.6%) 1.9 (0.2,6.8)	0 0.0 (0.0,10.6)	2 (2.1%) 1.4 (0.2,5.1)	0 0.0 (0.0,5.2)	0 0.0 (0.0,530.5)	0 0.0 (0.0,5.2)
TE Death	1 (1.3%) 0.9 (0.0,5.3)	0 0.0 (0.0,10.6)	1 (1.0%) 0.7 (0.0,4.0)	0 0.0 (0.0,5.2)	0 0.0 (0.0,530.5)	0 0.0 (0.0,5.2)
All Deaths	3 (3.9%) 2.8 (0.6,8.3)	0 0.0 (0.0,10.6)	3 (3.1%) 2.1 (0.4,6.2)	0 0.0 (0.0,5.2)	0 0.0 (0.0,530.5)	0 0.0 (0.0,5.2)
TEAE Leading to Premature Discontinuation of Study Drug	15 (19.5%) 14.2 (7.9,23.3)	2 (10.0%) 5.7 (0.7,20.7)	17 (17.5%) 12.1 (7.0,19.3)	2 (3.6%) 2.8 (0.3,10.2)	1 (33.3%) 143.8 (3.6,801.2)	3 (5.2%) 4.2 (0.9,12.2)
TEAE Leading to Temporary Interruption of Study Drug	28 (36.4%) 26.4 (17.6,38.2)	7 (35.0%) 20.1 (8.1,41.3)	35 (36.1%) 24.8 (17.3,34.6)	13 (23.6%) 18.3 (9.8,31.4)	0 0.0 (0.0,530.5)	13 (22.4%) 18.2 (9.7,31.1)

(Continued)	Adalimumab + MTX (N=325) PYE=290.1 n (%) EAIR (95% CI)	MTX Monotherapy (N=416) PYE=356.2 n (%) EAIR (95% CI)	Placebo (N=781) PYE=302.4 n (%) EAIR (95% CI)
eGFR at Baseline: 30 <= eGFR <60 mL/min/1.73 m^2	10	19	28
TEAE	10 (100.0%) 109.6 (52.5,201.5)	18 (94.7%) 100.7 (59.7,159.1)	17 (60.7%) 157.8 (91.9,252.6)
TEAE Related to Study Drug	5 (50.0%) 54.8 (17.8,127.8)	9 (47.4%) 50.3 (23.0,95.6)	1 (3.6%) 9.3 (0.2,51.7)
TEAE with Grade 3 or Higher	3 (30.0%) 32.9 (6.8,96.0)	2 (10.5%) 11.2 (1.4,40.4)	1 (3.6%) 9.3 (0.2,51.7)
TEAE Related to Study Drug with Grade 3 or Higher	2 (20.0%) 21.9 (2.7,79.1)	0 0.0 (0.0,20.6)	0 0.0 (0.0,34.2)
TE Serious AE	2 (20.0%) 21.9 (2.7,79.1)	3 (15.8%) 16.8 (3.5,49.0)	4 (14.3%) 37.1 (10.1,95.1)
TE Serious AE Related to Study Drug	0 0.0 (0.0,40.4)	0 0.0 (0.0,20.6)	0 0.0 (0.0,34.2)
TE Serious AE Leading to Death	0 0.0 (0.0,40.4)	0 0.0 (0.0,20.6)	0 0.0 (0.0,34.2)
TE Death	0 0.0 (0.0,40.4)	0 0.0 (0.0,20.6)	0 0.0 (0.0,34.2)
All Deaths	0 0.0 (0.0,40.4)	0 0.0 (0.0,20.6)	0 0.0 (0.0,34.2)
TEAE Leading to Premature Discontinuation of Study Drug	2 (20.0%) 21.9 (2.7,79.1)	1 (5.3%) 5.6 (0.1,31.2)	2 (7.1%) 18.6 (2.2,67.1)
TEAE Leading to Temporary Interruption of Study Drug	4 (40.0%) 43.8 (11.9,112.2)	10 (52.6%) 55.9 (26.8,102.9)	5 (17.9%) 46.4 (15.1,108.3)

AE = adverse event; csDMARD = conventional synthetic disease-modifying antirheumatic drug; EAIR = exposure-adjusted incidence rate; eGFR = estimated glomerular filtration rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily; TE = treatment-emergent; TEAE = treatment-emergent adverse event

Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg q.d., filgotinib 200 mg q.d., adalimumab, MTX, or Placebo (with or without MTX or csDMARDs).

Adverse events were coded according to MedDRA Version 22.0. Severity grades were defined by or converted to the CTCAE Version 4.03.

Treatment-emergent events began on or after the first dose date of filgotinib 100 mg q.d., filgotinib 200 mg q.d., adalimumab, or other, and no later than the earlier date of either 30 days after the last dose date, or the first dose date of the switched treatment minus 1 day.

Source: Filgotinib RA ISS MAA 180 Days, Adhoc-MAA-Table 3.2

Concomitant csDMARD

Most As Treated Subjects in the Pooled Phase 2 and Phase 3 Safety Population were taking a csDMARD (including MTX) on the date of their first dose of study drug in the Phase 2 and Phase 3 parent studies (filgotinib 200 mg: 79.8%; filgotinib 100 mg: 90.0%; total filgotinib: 86.5%; adalimumab: 100.0%; and other: 94.2%). Overall, the percentage of As Treated Subjects in the Pooled Phase 2 and Phase 3 Safety Studies who experienced any AE or SAE was numerically lower for subjects who were taking filgotinib 200 mg in monotherapy, than in combination with MTX (Table 30).

Pregnancy, lactation and male fertility

Pregnancy

According to the applicant, based on findings in animals, filgotinib may cause foetal harm and is therefore contraindicated during pregnancy. Women of childbearing potential have to use effective contraception during and for at least 1 week after cessation of filgotinib treatment.

Embryo-fetal 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 fetuses. In addition, fetal 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.

Overall, 19 pregnancies were reported in the clinical development program for filgotinib through the data cutoff dates (Table 43). In clinical studies of filgotinib, male and female subjects of childbearing potential who engage in heterosexual intercourse must have agreed to use protocol-specified methods of contraception.

Table 43 Pregnancy Cases in the Filgotinib RA Clinical Development Program

Study ID	Filgotinib Dose	Age of Mother (years)	Contraception	Last Menstrual Period	Last dose of filgotinib	Filgotinib Exposure Time (days)[a]	Relevant Concomitant treatment	Previous Pregnancy	Contraceptive Adherence	Pregnancy Outcome
GLPG0634-CL-203	25 mg BID[b]	37	Barrier + spermicide	Day 16	Day 49	33	Methotrexate	1 pregnancy with normal outcome and 1 spontaneous abortion	Not reported	Spontaneous abortion (1st trimester)
	200 mg QD[b]	20	Oral contraceptive + abstinence	Day 81	Day 124	43	Methotrexate	None	Inconsistent use of contraceptive medication	Spontaneous abortion (1st trimester)
GLPG0634-CL-205	100 mg BID[b]	33	None	Day 915	Day 958	43	Methotrexate	2 pregnancies with normal outcomes and 1 missed abortion	Not reported	Birth of a healthy baby
	100 mg BID	24	Injectable contraceptive	Day 1152	Day 1180	28	Methotrexate	"Gravida 2, Para 2": 2 successful deliveries	Not reported	Spontaneous abortion (2nd trimester)
	200 mg QD	34	Oral contraceptive	Day 1301	Day 1308	NA	None	None	Not reported	Birth of a healthy baby
	200 mg QD[b]	25	Oral contraceptive	Day 257	Day 282	25	None	1 pregnancy with normal outcome	Not reported	Birth of a baby with a congenital abnormality
	200 mg QD[b]	34	Oral contraceptive + barrier	Day 960	Day 1014	46[c]	Valproate	2 pregnancies with normal outcomes (1 with twins)	Not reported	Spontaneous abortion (1st trimester)

Study ID	Filgotinib Dose	Age of Mother (years)	Contraception	Last Menstrual Period	Last dose of filgotinib	Filgotinib Exposure Time (days)[a]	Relevant Concomitant treatment	Previous Pregnancy	Contraceptive Adherence	Pregnancy Outcome
GS-US-417-0301	100 mg QD	33	Intrauterine contraceptive device + barrier + spermicide	Day 24	Day 84	60	Methotrexate	None	Not reported	Birth of a healthy baby
	100 mg QD	31	Barrier	Day 342	Day 366	23	None	1 successful delivery	Not reported	Elective abortion (1st trimester)
GS-US-417-0303	200 mg QD	38	Barrier + spermicide	Day -4	Day 43	45	None	"Gravida 4, Para 2": 2 successful deliveries and 1 spontaneous abortion	Not reported	Loss to follow-up
GS-US-417-0304	200 mg QD	28	Barrier + unspecified contraception medication	Day 58	Day 83	25	None	"Gravida 3, Para 3": 3 successful deliveries	Not reported	Spontaneous abortion (1st trimester)
	200 mg QD	25	Barrier + unspecified contraceptive medication	Day 103	Day 140	37	None	1 successful delivery	Inconsistent use of contraceptive medication	Birth of a healthy baby
	200 mg QD	21	Barrier + unspecified contraceptive medication	Day 36	Day 58	22	None	Not reported	Not reported	Birth of a healthy baby
	100 mg QD	31	Barrier + timing method	Day 44	Day 84	40	Methotrexate	"Gravida 2, Para 2": 2 successful deliveries	Not reported	Spontaneous abortion (1st trimester)
	200 mg QD	22[d]	Barrier + periodic abstinence	Day 175	Day 204	29	Methotrexate	None	Not reported	Birth of a healthy baby
	100 mg QD	30	No information provided	Day -10	Day 43	51	Methotrexate	"Gravida 1, Para 1": 1 successful	Not reported	Spontaneous abortion (1st trimester)

Study ID	Filgotinib Dose	Age of Mother (years)	Contraception	Last Menstrual Period	Last dose of filgotinib	Filgotinib Exposure Time (days)[a]	Relevant Concomitant treatment	Previous Pregnancy	Contraceptive Adherence	Pregnancy Outcome
								delivery		
	200 mg QD	27[d]	Barrier + periodic abstinence	Day 208	Day 215	7	None	"Gravida 2, Para 2": 2 successful deliveries	Not reported	Pending
	200 mg QD	21	Injectable contraceptive + barrier	Day 218	Day 247	29	None	None	Inconsistent use of contraceptive medication	Pending
	200 mg QD	43	Intrauterine device	Day 51	Day 85	34	None	"Gravida 3, Para 2": 2 successful deliveries and 1 spontaneous abortion	Not reported	Ectopic pregnancy

ID = identification; NA = not applicable; RA = rheumatoid arthritis
a Filgotinib exposure during pregnancy. Filgotinib exposure during pregnancy is defined as days from the mothers' last menstrual period to filgotinib stop date or abortion date, whichever occurred first. If not specified, filgotinib was discontinued prior to abortion.
b The pregnancies occurred in Galapagos-specified contraception requirements.
c The subject had spontaneous abortion on 17 September 2017 prior to discontinuation of filgotinib.
d Calculated based on the date of birth and last menstrual period.
Source: Gilead Global Safety database (data on file)

Among these 19 pregnancies, 16 have a known outcome. In 3 remaining cases, there are 2 ongoing pregnancies and 1 lost of follow-up.

Among 16 pregnancies, issues are distributed as follows:

- 1 ectopic pregnancy

- 1 elective termination

- 7 live births including 1 case with a malformation

- 7 spontaneous abortion. A concomitant medication is specified in 6 cases : 5 with methotrexate and 1 with valproate

Lactation

In animal studies, filgotinib was detected in the plasma of nursing rat pups likely due to the presence of filgotinib in milk. It is not known if filgotinib is secreted in human breast milk. According to the applicant, a risk to the breast-fed child cannot be excluded and therefore filgotinib should not be used during breast-feeding.

Male fertility

In animal studies, decreased fertility, impaired spermatogenesis and histopathological effects on male reproductive organs were observed. These effects are currently being investigated in ongoing studies in human males (MANTA [Study GS-US-418-4279] and MANTA-RAy [Study GLPG0634-CL-227]).

Immunological events

Not applicable for a small molecule.

Safety related to drug-drug interactions and other interactions

According to the applicant, filgotinib is primarily metabolized by carboxylesterase (CES)2 and CES1, and is not a clinically relevant inhibitor or inducer of enzymes or transporters commonly involved in drug interactions such as cytochrome P450 enzymes (CYP) and uridine diphosphate-glucuronyltransferases.

According to the applicant, in drug interaction studies conducted with filgotinib no clinically relevant DDIs were observed when filgotinib was combined with the following drugs: the combined oral contraceptive ethinyl estradiol and levonorgestrel, famotidine, itraconazole (P-glycoprotein [P-gp] inhibitor), metformin (OCT2/MATE1/MATE2K substrate), midazolam (CYP3A4 substrate), omeprazole, and rifampin (P-gp inducer).

Discontinuation due to AEs

Table 44 presents TEAEs leading to study drug discontinuation in pooled data from phase 2 and phase 3 studies.

Table 44. Adverse Events leading to discontinuation in the Pooled Safety Population (Safety Analysis Set, As Treated Subjects)

Number (%) of Subjects with Any	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE=290.1) n (%) EAIR (95% CI)	MTX Monotherapy (N=416) (PYE=356.2) n (%) EAIR (95% CI)	Placebo (N=781) (PYE=302.4) n (%) EAIR (95% CI)
	+ csDMARDs (N=1817) (PYE=3003.3) n (%) EAIR (95% CI)	Monotherapy (N=450) (PYE=1044.4) n (%) EAIR (95% CI)	Total (N=2267) (PYE=4047.7) n (%) EAIR (95% CI)	+ csDMARDs (N=1494) (PYE=1964.7) n (%) EAIR (95% CI)	Monotherapy (N=153) (PYE=68.3) n (%) EAIR (95% CI)	Total (N=1647) (PYE=2032.9) n (%) EAIR (95% CI)			
TEAE Leading to Premature Discontinuation of Study Drug	164 (9.0%)	76 (16.9%)	240 (10.6%)	85 (5.7%)	10 (6.5%)	95 (5.8%)	18 (5.5%)	25 (6.0%)	24 (3.1%)
	5.5 (4.7,6.4)	7.3 (5.7,9.1)	5.9 (5.2,6.7)	4.3 (3.5,5.3)	14.6 (7.0,26.9)	4.7 (3.8,5.7)	6.2 (3.7,9.8)	7.0 (4.5,10.4)	7.9 (5.1,11.8)

AE = adverse event; csDMARD = conventional synthetic disease-modifying rheumatic drug; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; PYE = patient-years of exposure; QD = once daily; TE = treatment emergent; TEAE = treatment-emergent adverse event
Safety Analysis Set includes subjects who received at least 1 dose of study drug of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo (with or without MTX or csDMARDs).
Adverse events were coded according to MedDRA Version 22.0.
Severity grades were defined by or converted to the CTCAE Version 4.03.
Treatment-emergent events began on or after the first dose date of filgotinib 100 mg once daily, filgotinib 200 mg once daily, adalimumab, MTX, or placebo, and no later than the earlier date of either 30 days after the last dose date, or the first dose date of the switched treatment minus 1 day.
TEAEs leading to premature discontinuation or temporary interruption of study drug included subjects from GS-US-417-0303 that were discontinued or interrupted from MTX but continued filgotinib in filgotinib 200 mg once daily or filgotinib 100 mg once daily groups.
EAIR: Exposure-adjusted incidence rate per 100 PYE. Exact Poisson method was used to calculate the 95% CI {Ulm 1990}.

Post marketing experience

There is no post-marketing data available, since filgotinib is currently not approved anywhere.

2.6.1. Discussion on clinical safety

There are currently three JAK inhibitors approved for the treatment of RA; Xeljanz (tofacitinib), Olumiant (baricitinib) and Rinvoq (upadacitinib). The previously observed safety issues with JAK inhibitors include venous thromboembolism, neutropenia, infections (especially herpes zoster), lipid disorders, hepatotoxicity, gastrointestinal symptoms and elevated muscle enzymes. There has been concern on an increased risk for malignancies and cardiovascular events, and long-term studies are ongoing. There has also been concern on an increased risk for gastrointestinal perforations, although the exact role of JAK inhibition is currently not clear.

JAK inhibitors differ in their *in vitro* selectivity for JAK subtypes. Tofacitinib preferentially inhibits the *in vitro* activities of JAK1/JAK2, JAK1/JAK3, and to a lesser extent, JAK2/JAK2, while baricitinib more selectively inhibits the *in vitro* activities of JAK1/JAK2 and TYK2 compared with JAK3. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.

The clinical development program of filgotinib included five phase 2 studies (including one long-term extension) and four phase 3 studies (including one long-term extension) in over 3000 adults with RA including MTX-naive subjects (FINCH3), those with inadequate response to MTX (MTX-IR, FINCH1), and subjects with inadequate response or intolerance to bDMARDs (bDMARD-IR, FINCH2). For two of the phase 3 studies, FINCH1 and FINCH 3, interim data up to 24 weeks (October 2018) were presented in the original submission. Final data from the 52-week period were submitted in response to day 120 LoQ. For the third phase 3 study and phase 2 studies (FINCH2, DARWIN 1 and DARWIN 2), the final CSRs included 24-week data. Pooled data are presented from the phase 2 and phase 3 studies. This pooled population also includes subjects in the interim CSRs from the phase 2 long-term extension study DARWIN 3.

Subjects at high risk for cardiovascular disease, subjects with a history of malignancy or gastrointestinal perforations, and subjects with severe impairment of renal or liver function were excluded from the clinical studies.

In addition, filgotinib was initially proposed to be given either in monotherapy or in combination with MTX or other csDMARDs. Since data supporting the combination with csDMARDs other then MTX were not presented, this was raised as a major objection in the D120 LoQ. As a consequence, the proposal for use in combination with csDMARDs was withdrawn by the applicant with their responses to the D120 LoQ.

JAK inhibitors are known to be teratogenic, and filgotinib is proposed to be contraindicated during pregnancy (see Section 2.3.5.).

The adverse drug reactions proposed for labelling were infections (including urinary tract infection, upper respiratory tract infection, herpes zoster and pneumonia), neutropenia, dizziness, nausea, and increased blood creatine phosphokinase . Warnings were proposed for infections, malignancy, live vaccines, lipid derangements, and venous thromboembolism.

During the first 12 weeks (pooled data from phase 2 and phase 3 studies), adverse events were reported for 658/1403 (47%) of subjects treated with filgotinib 200 mg, 442/995 (44%) of subjects treated with filgotinib 100 mg, 130/325 (40%) of subjects treated with adalimumab and 522/1197 (44%) of subjects in the "other" (MTX, other csDMARD or purely placebo) arms. The most common adverse events were nasopharyngitis, upper respiratory tract infection, nausea, headache, hypertension, urinary tract infection and bronchitis. Serious adverse events were reported less frequently for both filgotinib arms than for adalimumab, and there were no dose-relation observed. There were two deaths in the filgotinib 200 mg arm; 1 septic shock secondary to pneumonia on day 25, and 1 lupus cardiomyopathy on day 7. There was 1 death in the filgotinib 100 mg arm; a myocardial infarction on day 13.

In pooled data from the final phase 2 and 3 studies, adverse events were observed in a similar frequency for filgotinib 200 mg (1771/2267 patients, 78.1%, EAIR 43.8 E/100PY) and adalimumab (239/325 subjects, 73.5%, EAIR 82.4 E/100 PY), while the exposure-adjusted incidence rate was higher for adalimumab. Adverse events were less frequent for filgotinib 100 mg (1140/1647 subjects, 69.2%, EAIR 56.1E/100 PY). Exposure-adjusted incidence rates for the pooled data were presented in response to day 120 LoQ. The regimen dose 100 mg BID have been evaluated during phase 2, and the applicant was in the first LoQ requested to present the pooled data for this regimen in order to allow proper benefice/risk ratio comparison. Due to the few events, it is difficult to conclude regarding a tendency of difference in adverse events EAIR between 200 mg once daily and 100 mg BID arms. At this time, it seems there is no difference regarding safety between the 2 administration schemes; hence, the CHMP considered that the issue is solved.

FINCH3 includes a direct comparison between filgotinib 200 mg in combination with MTX and filgotinib 200 mg in monotherapy. The frequency of TEAEs was higher for filgotinib in combination with MTX (318/416 subjects, 76.4%) than for filgotinib in monotherapy (143/210 subjects, 68.1%) in the final 52-week data presented in response to day 120 LoQ. Although SAEs were observed less frequently in combination therapy, all deaths were observed when filgotinib was given in combination with MTX. The additional benefit gained by combining filgotinib with MTX was discussed in response to day 120 LoQ, when the Applicant argued that current evidence from randomized controlled studies and observational studies supports that there might be long-lasting, clinically meaningful benefit of initial, aggressive therapy with a combination of MTX and bDMARDs or tsDMARDs versus MTX monotherapy. This was agreed by the CHMP.

Adverse events of special interest included major adverse cardiovascular events (MACE), infections (including serious infections, herpes zoster, TB, opportunistic infections and hepatitis B or C infections), venous thromboembolism (deep vein thrombosis or pulmonary embolism), malignancy and gastrointestinal perforations.

MACE

The exposure-adjusted incidence rate of MACE was higher for the filgotinib 200 mg group than for the adalimumab group, but lower than for the MTX monotherapy group. The EAIR was slightly higher for filgotinib 100 mg than for filgotinib 200 mg and thus, no dose-relation was seen.

In updated pooled data from phase 2 and phase 3 studies presented in response to day 120 LoQ, a total of 10 deaths from positively-adjudicated MACE was observed, all in filgotinib treatment groups. These 10 deaths were due to different aetiologies including lupus myocarditis, ischemic stroke, exudative pericarditis, myocardial infarction and subarachnoid haemorrhage, and no clear pattern was identified. In addition, there was 1 death due to pulmonary embolism and deep vein thrombosis in a patient switching from placebo to filgotinib 200 mg.

According to the applicant, a majority of the subjects had cardiovascular risk factor such as obesity, hypertension, hyperlipidaemia, or advanced age. At the CHMP's request, a warning on the cardiovascular risk was included in the Section 4.4 SmPC.

All infections

In pooled safety data from the final CSRs presented in response to day 120 LoQ, the frequency of infections was not higher for filgotinib 200 mg (26.5 E/100PY) or filgotinib 100 mg (31.9 E/100PY) than for adalimumab (44.5 E/100PY) or MTX (44.1 E/100PY). No dose-relation was seen, which is reassuring.

Serious infections

In pooled safety data from the final CSRs presented in response to day 120 LoQ, the exposure-adjusted incidence rate for serious infections was not higher for any filgotinib group than for adalimumab. The risk was numerically lower for filgotinib 200 mg than for filgotinib 100 mg.

At the CHMP's request, the Applicant included a contraindication for filgotinib in patients with active serious infections. In addition, at the CHMP's request, more detailed description regarding infections was included in sections 4.4 and 4.8 of the SmPC.

Pneumonia is a serious adverse event which have been proposed in section 4.8 of the draft SmPC. Following CHMP's request, the applicant presented the infectious agents involved in pneumonia and discussed if the risk might be prevented (vaccination). The presented data included too few cases to conclude regarding a predominant infectious agent, and the issue was considered solved by the CHMP. At the CHMP's request, a warning is included in Section 4.4 of the SmPC.

The applicant presented in response to the day 120 LoQ a review on the acute respiratory failure cases. The answers provided were considered satisfactory, and the applicant's proposal of monitoring through routine pharmacovigilance is endorsed.

Herpes zoster and varicella zoster

Herpes zoster was observed more frequently in filgotinib arms than in the adalimumab and MTX arms. Herpes zoster is proposed to be listed as an ADR in section 4.8 of the SmPC with a frequency uncommon; this is supported by the CHMP.

There were a total of 7 serious cases of herpes zoster – 5 in subjects receiving filgotinib 200 mg and 2 in subjects receiving filgotinib 100 mg. All 7 cases required hospitalisation. There were two cases reported of varicella zoster, both in the filgotinib 100 mg arm. At the CHMP's request, a warning is included in Section 4.4 of the SmPC.

In addition to these cases, there was one death (FINCH1) due to varicella. This case was further discussed in response to day 120 LoQ, and no SmPC update was considered needed by the CHMP.

Tuberculosis and other opportunistic infections

There were three cases of active TB in the filgotinib 100 mg group. All subjects screened negative in the QuantiFERON TB-Gold In-Tube test at entry into the parent studies, indicating there were no reactivation of TB. At the CHMP's request, filgotinib was contraindicated in patients with active tuberculosis and adequate information was included in Section 4.4 of the SmPC.

There were 3 cases of oesophageal candidiasis reported in filgotinib groups. Mentioning oesophageal candidiasis in SmPC section 4.4 was considered adequate by the CHMP.

Hepatitis B or C infections

In phase 2 studies, subjects with positive serology for hepatitis B or C were excluded from participation. In phase 3 studies, subjects with active HBC or HCV infection (as defined by positive HBsAg, HBV DNA or HCV RNA) were excluded while subjects with positive HBV core Ab and negative HBV DNA were allowed to participate, and were tested every 3 months for HBV DNA. At the CHMP's request, a warning on the risk for viral reactivation has been added in Section 4.4 of the SmPC.

Venous thromboembolism (deep vein thrombosis and pulmonary embolism)

VTE has been observed for the previously approved JAK inhibitors. In final pooled data presented in response to day 120 LoQ, there were 8 cases reported for filgotinib 200 mg and 1 case for filgotinib 100 mg, compared to 1 case reported for adalimumab and 2 cases for MTX. It is noted that the EAIR for venous thromboembolism is not higher for filgotinib than for adalimumab or MTX. Nonetheless, at the CHMP's request, a warning on the potential class effect of JAK inhibitors on the risk for venous thromboembolism has been added in Section 4.4 of the SmPC.

Malignancies (excluding non-melanoma skin cancer)

No firm conclusions can be drawn from the data due to the limited exposure so far, although it is reassuring to the CHMP that the risk observed so far is not higher for filgotinib than for the comparators. The described malignancies include solid tumours as well as lymphomas. The risk also needs to be followed post-approval (see RMP –Section 2.7.). A warning in Section 4.4 of the SmPC was proposed which was acceptable to the CHMP.

Non-melanoma skin cancer

Although long-term data are limited, there have been cases of NMSC described with a possible dose-relation. A warning in Section 4.4 of the SmPC was proposed which was acceptable to the CHMP.

Gastrointestinal perforations

Subjects with a history of GI perforation were excluded from the phase 3 studies. Nonetheless, there were three cases of gastrointestinal perforation (duodenal/gastric/diverticular) in subjects treated with 200 mg filgotinib, as compared to no cases in the other groups. Of these, 2 were upper GI perforations and 1 was a lower GI perforation. There is previous concern on lower GI perforations in patients treated with interleukin-6 receptor antagonists and potentially with agents that have downstream effect on

interleukin-6 signalling. Gastrointestinal perforation is included as an important potential risk in the filgotinib RMP (see RMP – Section 2.7.). Based on this, the CHMP accepted not to include a warning in Section 4.4 of the SmPC but to continue the observation of this risk post-marketing.

Deaths

To date, there have been 19 deaths among filgotinib 200 mg-treated subjects and 6 deaths among filgotinib 100 mg-treated subject (pooled phase 2 and phase 3 studies). The causes of death include infections, venous thromboembolism, malignancies and cardiovascular events and no specific pattern could be observed other than what is expected in an RA population.

There seems to be an increased mortality for filgotinib 200 mg (19 events, 0.5 E/100 PY) than for filgotinibib 100 mg (6 events, 0.3 E/100 PYs), adalimumab (1 event, 0.3 E/100PY) and MTX monotherapy (0 events), although the comparison is hampered by the different exposure to the drugs. When compared to other RA clinical trial programs, the EAIR for death for filgotinib is comparable to the other approved JAK inhibitors, although limitations of inter-study comparisons are acknowledged.

The causes of death are expected given the known safety problems with JAK inhibitors; infections including meningitis, venous thromboembolism and cardiovascular disease. There were 6 cases of malignancies. The follow-up time is too short for firm conclusions with regards to malignancy; however, these cases occurred after quite long treatment (minimum 214 days).

There were two cases of death due to interstitial lung disease. The applicant presented further information on these cases in response to day 120 LoQ. Since causality could not be considered established, no SmPC update was considered needed by the CHMP.

In the final CSR from FINCH1, with a direct comparison between filgotinib and adalimumab on top of MTX, there were 3 deaths/475 subjects for filgotinib 200 mg (0.6%, these were 2 cases of septic shock due to pneumonia and 1 case of alveolitis and respiratory failure), 1/480 (0.2%, this was a myocardial infarction) for filgotinib 100 mg and 1/325 (0.3%, sepsis) for adalimumab. There was one additional death for filgotinib 200 mg (+MTX) in a subject who switched from placebo; a case of ischemic stroke, DVT and pulmonary embolism on day 224 (switched after 24 weeks, approx. day 168). The comparison between filgotinib and adalimumab (on top of MTX) is highly clinically relevant. Although the numbers are small there seems to be a numerical difference with an increased incidence of death for filgotinib 200 mg in combination with csDMARDs, compared to the 100 mg dose and to adalimumab. Even if the absolute risk is small, the relative risk is doubled compared to the 100 mg dose. Therefore, the applicant was asked to discuss the strength of the evidence supporting this imbalance in mortality and to justify that the benefits of the 200 mg dose outweigh the increased risk. In this context, the Applicant was asked to discuss which implications an increased risk of mortality might have post-approval when filgotinib may be used in a wider population than the population included in the clinical development programme (where for example patients at high cardiovascular risk were excluded).

In response to this major objection, the applicant discussed the numerical difference in mortality for the filgotinib 200 mg dose compared to the 100 mg dose and to adalimumab. With regards to the observed mortality difference between filgotinib (0.5 E per 100 PYE) and adalimumab (0.3 E per 100 PYE), the CHMP agreed with the applicant that the exposure to adalimumab in filgotinib clinical studies is low and that this influences the ability to achieve an accurate estimate of mortality rates.

As stated by the applicant, the main causes of death among patients with RA are CVD, infection, respiratory disease, and cancer. In the presented data, the exposure-adjusted incidence rates for deaths due to CV, and serious infections were similar across all treatment group. A numerically higher rate of mortality due to malignancies were observed for filgotinib 200 mg (6 cases, 0.1E/100PYE) compared to

other treatments (OE). The 6 on-study reported deaths due to malignancies were diverse, including non-Hodgkin's lymphoma, metastatic adenocarcinoma of the lung, squamous cell carcinoma of the esophagus, ovarian cancer, and unknown primary. The applicant states that two additional deaths, one in the placebo group (fatal malignant glioma) and one in the MTX group (small cell lung cancer), were reported after the subjects had left the study. When looking at all cases of malignancies (excluding non-melanoma skin cancer), there is no dose-dependency observed. Similarly, no dose-dependence is observed for the AESIs of serious infectious AEs or MACE which is reassuring.

The applicant has also discussed potential implications when filgotinib may be used in a wider population than was enrolled in clinical trials. The filgotinib RA clinical program excluded subjects with uncontrolled heart failure (New York Heart Association class 3 or 4), cerebrovascular accident, or myocardial infarction within the last 6 months before screening. However, these exclusion criteria have been used in most RA clinical trials. According to the applicant, extrapolating clinical trial findings to a wider RA population is challenging given the multifaceted nature of the disease, disease heterogenicity, and the interplay of disease activity and DMARDs on safety outcomes in RA. Usually clinical trial subjects have higher disease activity than the common RA population, and a lower mortality rate might be expected in the overall RA population. However, any potential for a lower mortality rate might be offset by the advanced age in the wider RA population. The risk of filgotinib in a wider RA population will be evaluated post-marketing. Meanwhile, the CHMP considered that the applicant has adequately minimized the risk through warnings and precautions in the SmPC.

Finally, the applicant has presented a benefit-risk discussion for the filgotinib 200 mg dose. From the presented data, the CHMP agreed that additional benefit of filgotinib is observed at the 200 mg dose over the 100 mg dose. There is a small numerical difference in mortality point estimates; however, the relevance of this observation is difficult to assess taken into account that overall the differences between all the analyzed treatment groups are small with overlapping 95% CIs and that there are no dose-dependency observed for the most important AESIs of serious infections, MACE or malignancy. In conclusion, the CHMP considered that the data supports the approval of the 200 mg-dose.

Laboratory findings

In pooled data from phase 2 and 3 studies, the proportion of subjects with grade 3 anaemia was similar in the filgotinib and adalimumab group, and higher in the "other" arm (placebo ± MTX or csDMARDs, and MTX monotherapy) during the first 12 weeks. The Hb levels seem to increase over time, probably reflecting a decreased inflammatory burden.

Decreased lymphocytes, total leukocytes and neutrophils was observed more frequently in filgotinib-treated subjects than in other groups. Neutropenia is proposed to be listed as an ADR in section 4.8 of the SmPC with a frequency uncommon which is acceptable. At the CHMP's request, monitoring recommendation has been added to section 4.2 of the SmPC.

Lipids

A dose-dependent increase in total cholesterol, and triglycerides were observed for filgotinib (pooled data from phase 2 and 3). Information is included in the SmPC in sections 4.2, 4.4. and 4.8 of the SmPC, which is acceptable to CHMP.

Renal and liver parameters

Increases in serum creatinine was very rare, and creatinine levels remained stable over time.

During the first 12 weeks, ALAT elevations were less common in the filgotinib group than in the adalimumab group, and ASAT elevation were comparable between the groups. Grade 3 increases in ASAT/ALAT were balanced between the groups, but one subject in the filgotinib 200 mg group had a grade 4 increase in ASAT/ALAT compared to none in the comparator groups. Details on this case was presented in response to day 120 LoQ, but due to confounding factors and lack of information, causality with filgotinib was not considered established. The CHMP agreed with the applicant that treatment with filgotinib does not confer an increased risk for elevated liver enzymes than the comparators adalimumab+MTX or MTX. Hence, no SmPC update was considered needed.

The applicant was asked to review the cases of acute kidney injury and Cholelithiasis and discuss if they constitute signals and should be added to SmPC. The applicant considered that the cases involved subjects with risk factors for cholelithiasis condition (such as being female and age ≥ 40 years). This risk factors are also associated with higher prevalence of RA and cholelithiasis are not retrieved with methotrexate. The applicant was also asked to discuss if there is a pharmacologic mechanism which may explain the greater occurrence of cholelithiasis in filgotinib groups compared to methotrexate, and also present and discuss the time to onset of cholelithiasis in filgotinib and placebo arms. Due to few cases during the analysis period. Based on the data submitted, the CHMP agreed that it is not possible to conclude that filgotinib had a role in the occurrence of cholelithiasis. This is was therefore considered solved.

Safety in special populations

Age

The percentage of subjects in the pooled Phase 2 and Phase 3 safety studies who experienced any AE, SAE and serious infection was numerically higher in subjects ≥ 65 years of age compared with subjects < 65 years of age, in the filgotinib 200 mg group.

For patients treated with MTX monotherapy group, the EAIR of TEAE, TE serious AE, Infectious AE, Serious Infectious AE were not higher for subjects≥ 75 years of age as compared to subjects<75 years of age. For the filgotinib 200 mg +/-csDMARD all these EAIRs were higher for subjects≥ 75 years compared to subjects<75 years while the pattern was less distinct for the lower filgotinib dose group. For adalimumab, most of these EAIRs were higher in the oldest group. Thus, the effect of age on safety appears more prominent for the higher filgotinib dose as compared to MTX monotherapy and also, to some extent, compared to the lower filgotinib dose. All the three JAK—inhibitors previously approved for the RA-indication includes SmPC-wordings aimed to mitigate the risks in the elderly population. Since both the 100 mg and 200 mg doses of filgotinib have been demonstrated to be effective, the benefits of recommending the 200 mg dose to all elderly patients are not considered to outweigh the risks. Therefore, a starting dose of 100 mg is recommended for patients aged 75 or above (See also clinical pharmacology section 2.4.).

Renal and hepatic impairment

Filgotinib is primarily excreted in urine. Mild renal impairment had no impact on filgotinib PK when compared to subjects with normal renal function. Moderate and severe renal impairment modestly increased filgotinib exposure (AUC_{tau}) by 1.5-fold. No dose adjustment is necessary in subjects with mild or moderate renal impairment. In subjects with severe renal impairment the recommended dose of filgotinib is 100 mg. In patients with moderate renal impairment, a 1.96 fold increase of AUCeff is observed Therefore, a lower dose of 100 mg is recommended for patients with moderate renal impairment (See also clinical pharmacology section 2.4.).

Exposures of filgotinib were not significantly impacted by moderate hepatic impairment, and was not evaluated in subjects with mild hepatic impairment. No dose adjustment is necessary in subjects with mild or moderate hepatic impairment. Filgotinib has not been evaluated in subjects with severe hepatic impairment and is therefore not recommended for use in this patient population. This is adequately reflected in Section 4.2 of the SmPC (See also clinical pharmacology section 2.4). At the CHMP's request, the need for a contraindication was discussed and this was not considered needed because filgotinib is not primarily hepatically excreted and because there is no obvious effect on hepatic transaminases.

Concomitant csDMARDs and other drugs

As mentioned previously, data supporting the combination with csDMARDs other then MTX have not been presented. Therefore, at the CHMP's request, the indication was revised by the applicant to include only monotherapy or combination with MTX.

The applicant was in the first round invited to discuss potential interactions of filgotinib with other drugs, such as pivalate antibiotics and valproate, whose metabolic pathways also involve carnitine conjugation which may lead to secondary carnitine deficiency, but no such safety issue was found.

Pregnancy and lactation

Filgotinib is proposed to be contraindicated during pregnancy and should not be used during breast-feeding. This is adequately reflected in Sections 4.3 and 4.6 of the SmPC.

Although contraception was required during the clinical studies, it is noted that there were several pregnancies observed during the studies. In 6 of 19 pregnancies, a protocol-specified method was correctly used. The reason for this lack of efficacy is not entirely clear, since there are no expected drug interactions between filgotinib and oral contraceptives. At the CHMP's request, the Applicant discussed the reasons why contraception was not effective during the clinical studies, and whether this should warrant any further information in the SmPC, such as preferred contraceptive method. In view of the answers provided by the applicant and the information on pregnancy and contraception provided in the health care professionals brochure and patient card, the issue was considered solved. Section 4.6 of the SmPC recommends that "*Women of childbearing potential have to use effective contraception during and for at least 1 week after cessation of filgotinib treatment*."

Male fertility

In animal studies, decreased fertility, impaired spermatogenesis and histopathological effects on male reproductive organs were observed (see non-clinical Section 2.3). These effects are currently being investigated in ongoing studies in human males (MANTA [Study GS-US-418-4279] and MANTA-RAy [Study GLPG0634-CL-227]). The clinical consequences of these findings are currently uncertain. At the CHMP's request, the applicant presented blinded interim data from the MANTA study. The applicant has also reported results of hormone levels from phase 2 studies, in which there were no clinically relevant changes in sex hormone levels. The CHMP agrees with the applicant that current data suggest there is no clinically relevant effect of filgotinib on male reproductive hormones, including testosterone, FSH, LH, and inhibin B.

Interim data from the MANTA and MANTA-Ray studies will be submitted in first half of 2021. The findings in pre-clinical studies are of great concern and has not been seen for other JAK inhibitors. No mechanistic explanation has been identified, and thus there is a potential risk for humans. At the CHMP's request, a warning was included in section 4.4 of the SmPC and information on this risk in the proposed educational material.

2.6.2. Conclusions on the clinical safety

The major safety concern given the immunosuppressive effect of filgotinib is the risk for infections. The most commonly reported infections were mild (for example upper respiratory tract infections, nasopharyngitis and urinary tract infection), although also severe infections and deaths due to infections occurred. Filgotinib is contraindicated in active tuberculosis (TB) or active serious infections. Adequate warnings are included in Section 4.4 of the SmPC.

There is concern on an increased risk for venous thromboembolism for all agents in the JAK class. This is adequately addressed in the SmPC.

There is currently limited long-term data on the safety profile of filgotinib. Up to current cut-off, the exposure-adjusted incidence rate of death is higher for filgotinib 200 mg than for the comparator adalimumab, although the actual numbers are small. The relevance of this observation is difficult to assess taken into account that overall the differences between all the analysed treatment groups are small with overlapping 95% CIs and that there are no dose-dependency observed for the most important AESIs of serious infections, MACE or malignancy. The CHMP considered that those uncertainties would need to be followed-up post approval but were sufficiently addressed in the SmPC and the RMP.

The clinical consequences of pre-clinical findings on substantial decrease of fertility, impaired spermatogenesis and histopathological effects on male reproductive organs are unclear. These unexpected findings were observed already from 4 weeks of treatment and with low marginals and only partial recovery. The clinical consequences of these findings are being investigated in ongoing studies in human males (MANTA [Study GS-US-418-4279] and MANTA-RAy [Study GLPG0634-CL-227]). At the CHMP's request, the applicant has included warnings in the SmPC section 4.4, the package leaflet (PL) and in the educational material regarding the risk for infertility in male patients treated with filgotinib, aiming to limit the use of filgotinib to female patients and male patients without intent of fathering a child. This was considered acceptable to the CHMP until the results of the MANTA studies are available (1H21).

In conclusion, the CHMP considered that the safety profile of filgotinib was acceptable in view of the information included in the SmPC and RMP.

2.7. Risk Management Plan

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
Serious and opportunistic infections	*Routine risk communication:* SmPC section 4.2, 4.3, 4.4, 4.8 PL section 2 *Routine risk minimization activities recommending specific clinical measures to address the risk:* PL Section 2 provides guidance for the patient on signs and symptoms of infection and when to contact a healthcare professional. Section 4.3 of the SmPC contraindicates filgotinib in active TB and active serious infections. Recommendation in SmPC Section 4.2 to avoid initiation or interrupt treatment in patients with a serious infection, an absolute lymphocyte	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Serious and opportunistic infections adverse event follow-up form *Additional pharmacovigilance activities:* GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies GS-US-417-0304 (Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882,

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	count <0.5 x 10^9 cells/L or an absolute neutrophil count <1.0 x 10^9 cells/L. Recommendation in SmPC Section 4.4 on the management of infections in patients receiving filgotinib, and advice on patients at increased risk of infection. Recommendation in SmPC Section 4.4 to screen for tuberculosis (TB) and to initiate antimycobacterial therapy in patients with latent TB before administering filgotinib, and not to administer filgotinib to patients with active TB. Section 4.4 also provides advice on the management of viral reactivation, including Herpes zoster and viral hepatitis. Recommendation in SmPC section 4.8 that a starting dose of 100 mg is administered to patients aged 75 years and older as there was a higher incidence of serious infections in this age group, although data are limited.*Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA. *Additional risk minimization measures:* Healthcare professional guide, Patient Alert Card	GS-EU-417-5883 Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA in European registries
Herpes zoster	*Routine risk communication:* SmPC section 4.4, 4.8 PL section 2 *Routine risk minimization activities recommending specific clinical measures to address the potential risk:* Section 4.4 provides advice on the management of viral reactivation, including Herpes zoster. *Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA. *Additional risk minimization measures:* Healthcare professional guide, Patient Alert Card	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Varicella zoster virus (VZV) infection: Primary varicella (Chicken pox) or Herpes zoster (Shingles) follow-up form *Additional pharmacovigilance activities:* GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies GS-US-417-0304 (Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883 Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA in European registries
Important potential risk(s)		

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Embryolethality and teratogenicity	*Routine risk communication:* SmPC section 4.3, 4.6, 5.3 Package leaflet (PL) section 2 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Filgotinib is contraindicated in pregnancy. Recommendations on contraceptive measures to be taken by women of childbearing potential are included in SmPC section 4.6 and PL Section 2. *Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA. *Additional risk minimization measures:* Healthcare professional guide, Patient Alert Card	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Pregnancy Report Form Pregnancy Outcome Form *Additional pharmacovigilance activities:* None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Impaired spermatogenesis, leading to possible reduction in male fertility	*Routine risk communication:* SmPC section 4.4, 4.6, 5.3 PL section 2 *Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA. *Additional risk minimization measures:* Healthcare professional guide, Patient Alert Card	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Male Infertility follow-up form *Additional pharmacovigilance activities:* GS-US-418-4279 (MANTA) study to evaluate the testicular safety of filgotinib in adult males with IBD GLPG0634-CL-227 (MANTA RAy) study to evaluate the effect of filgotinib on semen parameters in adult males with rheumatic diseases
Malignancy	*Routine risk communication:* SmPC section 4.4 PL section 2 *Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Malignancy adverse event follow-up form *Additional pharmacovigilance activities:* GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies GS-US-417-0304 (Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883 Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA in European registries
Venous thromboembolism (deep venous thrombosis and pulmonary embolism)	*Routine risk communication:* SmPC section 4.4 PL section 2 *Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA. *Additional risk minimization measures:* Healthcare professional guide, Patient Alert Card	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Venous thromboembolism adverse event follow-up form *Additional pharmacovigilance activities:* GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies GS-US-417-0304 (Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883 Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA in European registries

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Gastrointestinal (GI) perforation	*Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Gastrointestinal perforation adverse event follow-up form *Additional pharmacovigilance activities:* GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies GS-US-417-0304 (Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883 Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA in European registries
Non-melanoma skin cancer (NMSC)	*Routine risk communication:* SmPC section 4.4 PL section 2 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Recommendation in section 4.4 for periodic skin examination for patients at risk of skin cancer. *Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Non-Melanoma Skin cancer adverse event follow-up form *Additional pharmacovigilance activities:* GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies GS-US-417-0304 (Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883 Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA in European registries
MACE	*Routine risk communication:* SmPC section 4.4 *Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA. *Additional risk minimization measures:* Healthcare professional guide, Patient Alert Card	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* MACE adverse event follow-up form *Additional pharmacovigilance activities:* GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies GS-US-417-0304 (Finch 4) long-term extension study in RA in subjects who received treatment in the parent

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		studies GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883 Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA in European registries
Hyperlipidemia	*Routine risk communication:* SmPC section 4.2, 4.4, 4.8 PL section 2 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Section 4.2 provides guidance on lipid monitoring and advice on the management of patients with hyperlipidaemia. *Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Hyperlipidaemia adverse event follow-up form *Additional pharmacovigilance activities:* GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies GS-US-417-0304 (Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883 Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA in European registries
Varicella zoster	*Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Varicella zoster virus (VZV) infection: Primary varicella (Chicken pox) or Herpes zoster (Shingles) follow-up form *Additional pharmacovigilance activities:* GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies GS-US-417-0304 (Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883 Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA in European registries
Missing information		
Use in patients with evidence of untreated chronic infection with hepatitis B or C	*Routine risk communication:* SmPC section 4.4 PL section 2	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		None *Additional pharmacovigilance activities:* None
Effect on vaccination efficacy	*Routine risk communication:* SmPC section 4.4 PL section 2 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Section 4.4 provides a recommendation that immunisations are updated in agreement with current guidelines before initiating treatment.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Use in the very elderly (>75 years)	*Routine risk communication:* SmPC section 4.2, 4.4, 4.8 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Section 4.2 provides advice that a starting dose of 100 mg qd is recommended for patients aged 75 years and above as clinical experience is limited. Section 4.4 advises that as there is a higher incidence of serious infections in the very elderly, caution should be used when treating this population. Section 4.8 advises that there was a higher incidence of serious infections in patients 75 years and older, although data are limited. *Additional risk minimization measures:* Healthcare professional guide	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies GS-US-417-0304 (Finch 4) long-term extension study in RA in subjects who received treatment in the parent studies GS-EU-417-9046, GS-EU-417-9047, GS-EU-417-9048, GS-EU-417-5882, GS-EU-417-5883 Non-interventional post-authorisation safety study of filgotinib in patients with moderate to severe active RA in European registries

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out

in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of filgotinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers filgotinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing statutory information via mobile scanning and other technologies has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

- Package leaflet
- Educational material for patients as outlined in the Risk Management Plan

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Jyseleca (filgotinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The initially proposed indication for this new JAK-inhibitor was:

"Jyseleca is indicated as monotherapy or in combination with methotrexate (MTX) or other conventional synthetic disease modifying antirheumatic drugs (csDMARDs) for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant to, one or more DMARDs.

Jyseleca is indicated as monotherapy for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have highly active and early progressive (erosive) disease, were not previously treated with MTX, and for whom treatment with MTX is inappropriate."

RA treatment should, according to relevant European recommendations (EULAR), generally be aimed at reaching a target of sustained low disease activity.

3.1.2. Available therapies and unmet medical need

Methotrexate (MTX) should, according to relevant European recommendations (EULAR), be the first treatment strategy for RA. In patients with contraindications to MTX (or early intolerance), leflunomide or sulfalazine should be considered as the (first) line treatment strategy. If there is no improvement by at most 3 months after start of treatment or the target has not been reached by 6 months, therapy should be adjusted. Depending on whether poor prognostic factors are present or not, other csDMARD or addition of a bDMARD (biologic DMARD) or tsDMARD (targeted synthetic DMARD) could then be considered. JAK-inhibitors are tsDMARD.

Despite the recent advances in this therapeutic field, there all still patients who either cannot tolerate or do not respond to the available treatment options i.e. there is still an unmet need.

3.1.3. Main clinical studies

The clinical development programme includes 4 Phase 2 studies in an MTX-IR population+ a long-term extension study and 3 pivotal phase III studies in MTX-IR, bDMARD-IR and MTX-naïve patients+ a long-term extension. The studies cover different aspects of the proposed indication and posology.

Phase II studies

Two completed, randomised, double-blind, placebo-controlled 4-week Phase 2a studies; GLPG0634-CL-201 (n=36, randomized) and GLPG0634-CL-202 (n=91, randomized), explored once or twice daily filgotinib doses up to a total daily dose of 200 mg or 300 mg on top of MTX, respectively. Doses above 200 mg daily were not pursued in Phase 2b because an exposure-response analysis was considered to have demonstrated that responses were at plateau with the 200-mg daily dose.

The randomised, double-blind, placebo-controlled phase 2b studies GLPG0634-CL-203; DARWIN 1 (n=594, randomized and treated) and GLPG0634-CL-204; DARWIN 2 (n= 283, randomized and treated) included subjects exposed at 3 different daily doses of GLPG0634 i.e. filgotinib (i.e., 50, 100, and 200 mg

daily) at 2 dose regimens (once and twice daily administration). Both studies; the first MTX-add on, the second monotherapy, were conducted in the MTX-IR population and were randomized, double-blind and placebo-controlled, with ACR 20 at week 12 being the primary endpoint and an NRI-approach. The designs of the phase IIb dose-finding studies, including the selection of the primary endpoint, are generally considered acceptable to the CHMP.

Regarding DARWIN 2, it is noted that although this was considered as a monotherapy study, antimalarial DMARDs were included among the permitted medications.

Phase III studies

FINCH 1 is a randomised, double-blind, placebo and active-controlled MTX-add on study in which 1755 subjects from a second line population (active RA despite MTX-treatment) with poor prognostic factors were randomized and treated with either Filgotinib 100 mgx1, Filgotinib 200 mgx1, the TNF-inhibitor adalimumab or placebo. There was a rescue-possibility (to SOC) at week 14. In addition to MTX, concomitant anti-malarial csDMARDs were allowed but no other csDMARDs.

FINCH 2 is a randomised, double-blind, placebo-controlled, csDMARD-add on study in which 448 subjects from a third line population (failed or intolerant to at least 1 bDMARD) were randomized and treated with either Filgotinib 100 mgx1, Filgotinib 200 mgx1 or placebo with a rescue-possibility (to SOC) at week 14. Concomitant csDMARDs included MTX, hydroxychloroquine, sulfasalazine and leflunomide.

FINCH 3 is randomised, double-blind, active-controlled study in which 1249 subjects from a first line population (limited or no prior treatment with MTX) with at least one poor prognostic factor were randomized and treated with either Filgotinib 100 mgx1+MTX, Filgotinib 200 mgx1+MTX, Filgotinib 200 mgx1 monotherapy or MTX monotherapy with a rescue-possibility (to SOC) at week 24. Antimalarials are included among the permitted concomitant medications and thus the treatment arm referred to as the Filgotinib monotherapy arm is not a monotherapy arm in the strictest sense.

3.2. Favourable effects

Short term favourable effects-data up to week 24

Short term favourable effects supporting the different parts of the proposed indication were provided and are summarized under the different headings below. An effect vs placebo was seen across populations although response rates were lower the more treatment-experienced the patients were.

Effects in MTX-IR for combination with MTX

In DARWIN 1, the outcome of the primary endpoint, ACR 20 response at week 12, was: 44.2% in the placebo group (+MTX), 56.1% in Filgotinib 50 mgx1+MTX group, 63.5% in the Filgotinib 100 mgx1+MTX group, 68.6% in the Filgotinib 200 mgx1+MTX, 57.0% in the Filgotinib 25 mgx1+MTX group, 60.0% in the Filgotinib 50 mgx2+MTX group and 78.6% in the Filgotinib 100 mgx2 +MTX group (p-values<0.05 for the comparison vs placebo for the 100 mgx1, 200 mgx1 and 100 mgx2 groups). Dose-dependent responses were observed in the majority of these secondary efficacy parameters including proportion of subjects achieving remission/LDA.

In FINCH 1, all superiority or noninferiority tests of filgotinib versus comparator in the hierarchical testing demonstrated a statistically significant superiority or noninferiority of filgotinib over the comparator ($p < 0.001$), with the exception of the final noninferiority test of the percentages of subjects who achieved DAS28(CRP) $\leq$ 3.2 at Week 12 (filgotinib 100 mg vs adalimumab; $p = 0.054$).

For the primary endpoint, ACR 20 at week 12, the proportion of responders were 76.6% in the Filgotinib 200 mgx1 (+MTX) group, 69.8% in the Filgotinib 100 mgx1(+MTX) group, 70.8% in the Adalimumab (+ MTX) group and 49.9% in the placebo (+ MTX) group (p<0.001 for both superiority comparisons between the Filgotinib groups and the placebo group).

For the key secondary endpoint LDA (defined as DAS28 (CRP)≤3.2) at week 12, the proportion of responders were 49.7% in the Filgotinib 200 mgx1(+MTX) group, 38.8% in the Filgotinib 100 mgx1(+MTX) group, 43.4% in the adalimumab (+ MTX) group and 23.4% in the placebo (+ MTX) group (p<0.001 for both superiority comparisons between the Filgotinib groups and the placebo group) and for the non-inferiority comparison of Filgotinib 200 mg group vs the adalimumab group). Non-inferiority of Filgotinib 200 mg vs adalimumab for DAS28(CRP) <= 3.2 at Week 12 was confirmed also in the Per-Protocol analysis.

For the key secondary endpoint, the proportion of subjects who achieve Remission defined as DAS28 (CRP)<2.6 at Week 24, the proportion of responders were 48.4% in the Filgotinib 200 mg (+ MTX) group, 35.2% in the Filgotinib 100 mg (+ MTX) group, 35.7% in the Adalimumab (+ MTX) group and 16.2% in the placebo (+ MTX) group (p<0.001 for both superiority comparisons between the Filgotinib groups and the placebo group).

For the key secondary endpoint, change from Baseline in mTSS at Week 24, the mean (SD) was 0.13 (0.937) in the Filgotinib 200 mg (+ MTX) group, 0.17 (0.905) in the Filgotinib 100 mg (+ MTX) group, 0.16 (0.948) in the Adalimumab group (+ MTX) and 0.38 (1.408) in the Placebo (+ MTX) group (p<0.001 for both superiority comparisons between the Filgotinib groups and the placebo group).

Numerically better outcomes were reported for both doses of Filgotinib compared to placebo for the CRP-independent outcome CDAI.

Regarding longer time efficacy, at week 24, the number of ACR 20 responders in absolute numbers increased vs week 12 in all groups but in particular in the placebo group. This was true also for the numbers of subjects that achieved DAS28 (CRP) <2.6 and DAS28 (CRP) <= 3.2 at week 12 vs week 24.

Effects in MTX/csDMARD-IR for monotherapy

In DARWIN 2, the outcome of the primary endpoint, ACR 20 response at week 12, was: 29.2% in the placebo group, 66.7% in the Filgotinib 50 mgx1 group, 65.7% in the Filgotinib 100 mgx1 group and 72.5% in the Filgotinib 200 mgx1 group (p<0.0001 for all comparisons vs placebo). The outcome for the secondary endpoint DAS28 (CRP) Remission or LDA at Weeks 12 (NRI [ITT Population]) was as follows at week 12: 13.9% in the placebo group, 23.6% in the Filgotinib 50 mgx1 group, 27.1% in the Filgotinib 100 mgx1 group and 44.9% in the Filgotinib 200 mgx1 group (p-value<0.05 for the comparison of the 200 mg group vs placebo). At week 24 the proportion with DAS28 (CRP) Remission or LDA was 34.7% in the Filgotinib 50 mgx1 group, 50.0% in the Filgotinib 100 mgx1 group and 42.0% in the Filgotinib 200 mgx1 group.

The overall results were not changed when subjects taking antimalarials were excluded from the analysis.

Effects in bDMARD-IR for combination with csDMARD

In FINCH 2, Filgotinib 200 mgx1 (+csDMARD) or 100 mgx1 (+ csDMARD) showed superiority over placebo (+csDMARD) for the primary endpoint and all key secondary endpoints.

The proportion that attained the primary endpoint, ACR 20 at week 12, was 66.0% in the Filgotinib 200 mgx1 (+csDMARD) group, 57.5% in the Filgotinib 100 mg (+csDMARD) group and 31.1% in the placebo (+csDMARD) group (p<0.001 for both the comparison between the Filgotinib groups and placebo).

For the key secondary endpoint, proportion of subjects who achieved LDA defined as DAS28(CRP) ≤ 3.2 at Week 12, it was 40.8% in the Filgotinib 200 mgx1 (+csDMARD) group, 37.3% in the Filgotinib 100 mgx1 (+csDMARD) group and 15.5% in the placebo (+csDMARD) group ($p < 0.001$ for both comparisons with placebo).

Differences vs placebo was seen for both doses with regards to the CRP-independent measure CDAI.

Numerically better improvements were seen Filgotinib vs placebo for primary and key secondary endpoints from week 2-4 through week 24.

Effects in MTX-naïve for combination with MTX and monotherapy

In FINCH 3, for the primary endpoint the superiority of filgotinib 200 mg + MTX over MTX monotherapy on the ACR20 response rate at Week 24 was formally demonstrated. Moreover, Filgotinib 200 mg + MTX and Filgotinib 100 mg + MTX demonstrated superiority over MTX monotherapy for ACR20, HAQ-DI, and DAS28(CRP) < 2.6 at Week 24.

For the primary endpoint, ACR 20 response at week 24, this was reached by 81.0% in the Filgotinib 200 mgx1+MTX group, 80.2% in the Filgotinib 100 mg x1+MTX group, 78.1% in the Filgotinib 200 mg monotherapy group and 71.4% in the MTX monotherapy group ($p<0.05$ for the two comparisons between Filgotinib combination therapy vs MTX). The results were not substantially changed when subjects taking antimalarials were excluded from the analysis.

For the key secondary endpoint proportion with DAS28(CRP) < 2.6 i.e. Remission at Week 24, this was achieved by 54.1% in the Filgotinib 200 mg 1x1 + MTX group, 42.5%, in the Filgotinib 100 mg 1x1+MTX, 42.4% in the Filgotinib 200 mg monotherapy group and 29.1% in the MTX monotherapy group ($p < 0.001$ for the comparisons with the two Filgotinib combination groups and MTX monotherapy group respectively).

For the key secondary endpoint change from baseline in the mTSS at Week 24, the mean (SD) was 0.20 (1.682) in the Filgotinib 200 mg group, 0.22 (1.530) in the Filgotinib 100 mg group, -0.04 (1.710) in the Filgotinib 200 mg monotherapy group and 0.52 (2.892) in the MTX monotherapy group.

Mean improvement from baseline to week 24 in the CRP-independent measure CDAI was numerically higher for each filgotinib group versus MTX monotherapy.

Numerically greater ACR20 response rates versus MTX monotherapy were seen from Week 2 for the Filgotinib groups and through Week 24. This was observed also for the proportion of subjects in remission (DAS28 CRP<2.6).

Long-term favourable effects

Effect in MTX/csDMARD-IR for combination with MTX and monotherapy

From the week 156- interim CSR of DARWIN 3, the long term follow-up that included MTX/csDMARD-IR subjects that received filgotinib monotherapy (n = 242, rolled over from parent phase II study DARWIN 2) or Filgotinib with MTX (n = 497, rolled over from parent phase II study DARWIN 1), there are indications that the treatment effect of filgotinib (as monotherapy or in combination with MTX) is maintained for up to 3 years in patients. It is noted that 229/491 MTX-IR subjects in the MTX + Filgotinib group had low disease activity at baseline and 200/290 subjects had Low disease activity at week 156. For the monotherapy group, the numbers were 97/234 and 88/136.

In response to the Day 120 LoQ, the final CSR for FINCH 1 with week 52-data was provided. The absolute number of responders in the Filgotinib 200 mg-group increased from week 12 to week 24 and did not

decrease from week 24 to week 52. For the Filgotinib 100 mg group and the adalimumab group, a similar pattern was seen. The ACR 20 response increased among placebo subjects that had been reassigned to receive Filgotinib (at Week 24). For LDA, the absolute number of responders increased in all treatment groups through week 12-24-52. Also with regards to remission, the absolute number of subjects increased from week 24 to week 52 in all three active treatment groups.

In response to the RSI, radiological measurements up to week 52 were provided and are reflected in the product information.

Effects in MTX-naïve for combination with MTX and monotherapy

In response to the Day 120 LoQ, the final CSR for FINCH 3 with week 52-data was provided. In all four treatment groups there was a slight decrease in the absolute number of ACR 20 responders from week 24 to week 52. In the Filgotinib + MTX arms, the absolute number in remission were essentially the same week 24 and week 52 while it increased somewhat from week 24 to week 52 in the Filgotinib mono-arm and the MTX arm.

In response to the RSI, radiological measurements up to week 52 were provided. At Week 52, a numerically greater proportion of subjects in the filgotinib 200 mg + MTX group had no radiographic progression compared with the MTX monotherapy group.

3.3. Uncertainties and limitations about favourable effects

The CHMP questioned the initially proposed indication "*[Tradename] is indicated as monotherapy for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have highly active and early progressive (erosive) disease, were not previously treated with MTX, and for whom treatment with MTX is inappropriate"* in the D120 LoQ in the light of the data submitted with this application, the totality of data on JAK-inhibitors that has so far become available and also considering that it would be the 1st in the class. The first line indication was withdrawn by the applicant with their responses to the D120 LoQ.

In addition, filgotinib was initially proposed to be given either in monotherapy or in combination with MTX or other csDMARDs. Since sufficient data supporting the combination with csDMARDs other then MTX were not presented, this was raised as a major objection in the D120 LoQ. As a consequence, the proposal for use in combination with csDMARDs was withdrawn by the applicant with their responses to the D120 LoQ.

3.4. Unfavourable effects

The major safety concern given the immunosuppressive effect of filgotinib is the risk for infections. During the first 12 weeks, the overall rate of infectious adverse events was 16.7% for filgotinib 200 mg, 15.3% for filgotinib 100 mg, 18.5% for adalimumab and 14.2% for MTX/csDMARDs/placebo group. The most commonly reported infections were upper respiratory tract infections, nasopharyngitis and urinary tract infection. During the same period, the rate of serious infections was 0.6% for filgotinib 200 mg, 0.8% for filgotinib 100 mg, 1.5% for adalimumab and 0.5% for MTX/csDMARDs/placebo group. In long-term data (up to 52 weeks), the incidence rate of infectious AEs was 26.5 E/100 PY for filgotinib 200 mg, 31.9 E/100PY for filgotinib 100 mg, 44.5 E/100PY for adalimumab and 44.1 E/100PY for MTX. Filgotinib is contraindicated in active serious infections. Adequate warnings are included in Section 4.4 of the SmPC.

Herpes zoster has been observed for other products in the class. The incidence rate for herpes zoster was 1.8 E/100PY for filgotinib 200 mg, 1.1 E/100PY for filgotinib 100 mg, 0.7 E/100 PY for adalimumab and 1.1 E/100PY for MTX. There were a total of 7 serious cases of herpes zoster – 5 in subjects receiving

filgotinib 200 mg and 2 in subjects receiving filgotinib 100 mg.. Adequate warnings are included in Section 4.4 of the SmPC.

There were three cases of active tuberculosis in the filgotinib 100 mg group. According to the applicant, there were no cases of reactivation of latent TB. Filgotinib is contraindicated in Active tuberculosis (TB) or active serious infections. Adequate warnings are included in Section 4.4 of the SmPC.

There is concern on an increased risk for venous thromboembolism for other JAK inhibitors. The incidence rate of VTE was 0.2 E/100PY for filgotinib 200 mg, 0 E/100PY for filgotinib 100 mg, 0.3 E/100 PY for adalimumab and 0.6 E/100PY for MTX. There have been two cases of death due to VTE in filgotinib-treated subjects. Adequate warnings are included in Section 4.4 of the SmPC.

Gastrointestinal perforations have been observed for JAK inhibitors, including also filgotinib. Currently, there have been three cases of gastrointestinal (gastric/duodenal/diverticular) perforation in the filgotinib 200 mg group, as compared to no cases in the other groups. The CHMP considered that the data didn't warrant the inclusion of a warning in Section 4.4 of the SmPC but this risk will be carefully followed-up post-marketing.

With regards to laboratory derangements, filgotinib is associated with a decrease in neutrophil counts. Increases of total cholesterol, triglycerides and LDL levels have been observed, while LDL/HDL ratios remained unchanged. Increases in creatinine kinas were more frequent for filgotinib than for the comparators. At the CHMP's request, monitoring recommendation has been added to section 4.2 of the SmPC.

JAK inhibitors are known to be teratogenic, and filgotinib is contraindicated during pregnancy.

3.5. Uncertainties and limitations about unfavourable effects

Important uncertainties relate to unfavourable effects of long latency and low frequency. Potential long-term unfavourable effects include:

Malignancies (excluding non-melanoma skin cancer): In the final data in phase 2/3 studies, there have been 22 cases of malignancies in filgotinib 200 mg-treated subjects and 11 cases in filgotinib 100 mg-treated subjects. The incidence rate of malignancies was 0.5 E/100PY for both filgotinib 200 mg and 100 mg, 0.7 E/100 PY for adalimumab and 1.1 E/100PY for MTX. The described malignancies include solid tumours as well as lymphomas. Adequate warnings are included in Section 4.4 of the SmPC and long-term data that will be provided post approval will be important to better assess this risk.

Major adverse cardiovascular events: Subjects at high risk for cardiovascular disease were excluded from the phase 3 studies. In the updated data up to week 52 in phase 2/3 studies, the incidence rate of MACE was 0.5 E/100PY for filgotinib 200 mg, 0.6 E/100PY for filgotinib 100 mg, 0.3 E/100 PY for adalimumab and 0.6 E/100PY for MTX. Adequate warnings are included in Section 4.4 of the SmPC and long-term data that will be provided post approval will be important to better assess this risk.

In animal studies, decreased fertility, impaired spermatogenesis and histopathological effects on male reproductive organs were observed. These effects are currently being investigated in ongoing studies in human males (MANTA [Study GS-US-418-4279] and MANTA-RAy [Study GLPG0634-CL-227]). The knowledge on the clinical consequences of these findings are currently very limited. Adequate warnings are included in Section 4.4 of the SmPC and in the educational material regarding the risk for infertility in male patients treated with filgotinib, aiming to limit the use of filgotinib to female patients and male patients without intent of fathering a child.

There are limited data in patients over 75 years of age and in patients with moderate renal impairment. In the available data, an increased risk for serious AEs is observed for the 200 mg compared to the 100

mg dose. Therefore, a starting dose of 100 mg is recommended to patients aged 75 or above. In patients with moderate renal impairment, a 1.96-fold increase of AUCeff is observed. Therefore, as for patients with severe renal impairment, a dose of 100 mg is recommended to patients with moderate renal impairment.

3.6. Effects Table

Table 45: Effects Table for Filgotinib for RA

Effect	Short Description	Unit	Filgotinib 200 mg+MTX/csDMARD	Filgotinib 100 mg+MTX/csDMARD	Filgotinib 200 ng mono	Control: Adalimumab+ MTX	Control:placebo+MTX/csDMARD/MTX mono	Uncertainties/ Strength of evidence	References
			Favourable Effects						
ACR 20 Response									
ACR 20 week 12, MTX-IR	Response rate, primary endpoint	% (95% CI)	76.6% (72.7%; 80.5%)	69.8% (65.6%; 74.0%)		70.8% 65.7%;75.9%)	49.9% (45.3%;54.5%)		FINCH 1
ACR 20 week 12, bDMARD-IR	Response rate, primary endpoint	%	66.0% (58.0%;74.0%)	57.5% (49.4%, 65.7%)			31.1% (23.3%, 38.9%)		FINCH 2
ACR 20 week 24, MTX-naive	Response rate, primary endpoint	%	81.0% (77.1%;84.9%)	80.2% (74.5%;85.9%)	78.1% (72.3%;83.9%)		71.4% (66.9%;75.9%)		FINCH 3
Target disease state									
LDA week 12, MTX-IR	DAS28≤3.2, most relevant key secondary endpoint	% (95% CI)	49.7% (45.1%;54.3%)	38.8% (34.3%; 43.2%)		43.4% (37.8%;48.9%)	23.4% (19.5%;27.3%)		FINCH 1
LDA week 12, bDMARD-IR	DAS28⩽3.2, most relevant key secondary endpoint	%	40.8% (32.5%; 49.1%)	37.3% (29.3%; 45.2%)			15.5% (9.4%; 21.7%)		FINCH 2
Remission week 24, MTX-naive	DAS28≤2.6, most relevant key secondary endpoint	%	54.1% (49.2%; 59.0%)	42.5% (35.5%, 49.5%)	42.4% (35.5%;49.3%)		29.1% (24.6%; 33.6%)		FINCH 3
Structural damage									

Effect	Short Description	Unit	Filgotinib 200 mg+MTX/csDMARD	Filgotinib 100 mg+MTX/csDMARD	Filgotinib 200 ng mono	Control: Adalimumab+ MTX	Control:placebo+MTX/csDMARD/MTX mono	Uncertainties/ Strength of evidence	References
Change mTSS week 24, MTX-IR	Radiographic progression, mean change (SD)		0.13 (0.937)	0.17 (0.905)		0.16 (0.948)	0.38 (1.408)		FINCH 1
Change mTSS Week 24, MTX-naive	Radiographic progression, mean change (SD)		0.20 (1.682)	0.22 (1.530)	−0.04 (1.710)		0.52 (2.892)		FINCH 3

Effect	Short Description	Unit	Filgotinib 200 mg	Filgotinib 100 mg	Control: Adalimumab+ MTX	Control: placebo+MTX/csD MARD/MTX mono	Uncertainties/ Strength of evidence	References
Unfavourable effects								
Adverse events	Up to week 12	%	46.9	44.4	40	43.6	Short-term data. Randomised controlled data.	CSS table 7
Serious adverse events	Up to week 12	%	2.4	2.7	2.8	1.8	Short-term data. Randomised controlled data.	CSS table 7
Infections	Up to week 24	E/100PY	30.6	42.5	46.7	52.3	Exposure-adjusted	CSS table 22
Serious infections	Up to week 24	E/100PY	2.0	3.1	4.0	2.2	Exposure-adjusted	CSS table 23
Herpes zoster	Up to week 52	E/100PY	1.8	1.1	0.7	1.1 (MTX)	Exposure-adjusted	Response to MO day 120
Venous thrombo-embolism	Up to week 52	E/100PY	0.2	0	0.3	0.6 (MTX)	Exposure-adjusted	Response to MO day 120
MACE	Up to week 52	E/100PY	0.5	0.6	0.3	0.6 (MTX)	Exposure-adjusted	Response to MO day 120
Deaths	Up to week 52	E/100PY	0.5	0.3	0.3	0.3 (MTX)	Exposure-adjusted. Small numbers.	Response to MO day 120

Abbreviations: CSS: Summary of clinical safety. ISS: Integrated summary of safety. MTX: Methotrexate. MACE: Major adverse cardiovascular events. E: Event. PY: Patient year.

3.7. Benefit-risk assessment and discussion

3.7.1.1. *Importance of favourable and unfavourable effects*

The different favourable effects of filgotinib (overall response measured by ACR 20, achieving disease target state, prevention of structural damage) across the populations targeted by the proposed indication, is provided under the headings below.

Short term favourable effects- Data up to week 24

Overall clinical response measured by ACR 20

ACR 20 response at week 12/24 was the primary endpoint in all phase IIb and phase III studies in the Filgotinib development programme. ACR 20 response is no longer the endpoint of choice according to current RA EMA guidelines and not consistent with current RA treat to target-policies as underlined in current RA EULAR recommendations. However, it is still of some value that across the studies and populations, clear differences that are considered as clinically relevant were observed between Filgotinib groups (that included both monotherapy and combination therapy) and placebo/MTX monotherapy groups regarding this endpoint. As expected, rates were lower the more treatment-experienced the patients were.

Reaching target disease state

Regarding the outcomes of the more important endpoints reflecting a target disease state, that were recommended in the CHMP Scientific Advice as well as in current EMA guideline, these also appear to support the efficacy of Filgotinib across studies and populations:

Effects in MTX-IR for combination with MTX: In FINCH 1, almost half of the subjects that were treated with Filgotinib 200 mgx1 (+MTX) achieved low disease activity; LDA, at week 12 compared to approximately ¼ of the subjects in the control arm that received placebo (+MTX). The difference is considered both clinically and statistically significant. The proportion of subjects reaching LDA was lower in the 100 mg arm than the 200 mg arm but still clearly higher than in the placebo arm. In the group that received the active comparator adalimumab (+MTX), the proportion of subjects that achieved LDA was somewhat numerically lower than in the Filgotinib 200 mg (+MTX) group but higher than in the Filgotinib 100 mg (+MTX) group. The non-inferiority of Filgotinib 200 mg (+MTX) vs adalimumab (+MTX) was confirmed both in the primary analysis and the peer protocol analysis. This is considered important given that adalimumab would be an appropriate treatment alternative to JAK-inhibitors in clinical practice.

Effects in MTX/csDMARD-IR for monotherapy: In DARWIN 2, the outcome for DAS28 (CRP) Remission or LDA at Weeks 12 was 13.9% in the placebo group, and 44.9% in the Filgotinib 200 mgx1 group. The difference between the groups appears both of a clinically relevant magnitude and statistically significant. The proportion reaching Remission or LDA was lower in the 100 mg group than the 200 mg group but again still clearly higher than in the placebo group.

Effects in bDMARD-IR for combination with csDMARD: In FINCH 2, the proportion of subjects who achieved LDA at Week 12 was 40.8% in the Filgotinib 200 mgx1 (+csDMARD) group, 37.3% in the Filgotinib 100 mgx1 (+csDMARD) group and 15.5% in the placebo (+csDMARD) group. The difference vs placebo was, for both tested doses of Filgotinib, of a clinically relevant magnitude and also statistically

significant. That approximately 2/5 patients that do not respond to bDMARD do indeed respond to Filgotinib is an important finding given that this is a group of patients for which the number of alternative future treatment options are rather limited.

Effects in MTX-naïve for combination with MTX and monotherapy: In FINCH 3, Remission at Week 24, was achieved by 54.1% in the Filgotinib 200 mg 1x1 + MTX group, 42.5%, in the Filgotinib 100 mg 1x1+MTX, 42.4% in the Filgotinib 200 mg monotherapy group and 29.1% in the MTX monotherapy group. For both Filgotinib groups the difference vs MTX monotherapy was considered statistically significant and also clinically relevant. However, the comparison between Filgotinib monotherapy and MTX monotherapy as well as the comparison between Filgotinib monotherapy and combination therapy could be considered of even more clinical importance. Filgotinib monotherapy was numerically better than MTX monotherapy although the difference was not considered statistically significant. Similarly, the Filgotinib combination with MTX was numerically better than Filgotinib monotherapy.

Prevention of structural damage

Regarding prevention of structural damage, in the MTX-IR population in FINCH 1, in the comparison of mean change from Baseline in mTSS at Week 24 on top of MTX, both Filgotinib doses were statistically superior to placebo. Compared to adalimumab (comparison not included in the hierarchical statistical testing procedure), Filgotinib (in both doses) appeared to have a similar capability of preventing structural damage.

In the MTX-naïve population with poor prognostic factors in FINCH 3, Filgotinib in combination with MTX did not seem to be better than Filgotinib monotherapy in preventing structural damage (although no formally statistically significant differences could be reported). There were numerically lower progressions in all three Filgotinib groups compared to in the MTX monotherapy group.

Taken together, the week 24 radiographic data from these two studies are of clear interest as an important goal of RA therapy is to limit structural progression.

Long term favourable effects- Beyond 24 weeks

The interim data from the on-going phase 2 open-label extension study DARWIN 3 (with no control arm) that was submitted with this application is considered to provide some support for maintenance of efficacy up to 1 year and beyond. Together with the week 52-data from the FINCH 1 study (in MTX-IR) and FINCH 3-data (in MTX-naïve), maintenance of effect of filgotinib (on a group level) is considered to have been sufficiently demonstrated.

The week 52 radiographic data provided in response to the D120 LoQ, was overall consistent with the week 24 data.

3.7.1.2. Importance of unfavourable effects

The major safety concern given the immunosuppressive effect of filgotinib is the risk for infections. The most commonly reported infections were mild (for example upper respiratory tract infections, nasopharyngitis and urinary tract infection), although also severe infections and deaths due to infections occurred. Infections are frequently observed in the RA population and it is an expected risk with all immunosuppressive drugs. The risk seems comparable to other JAK inhibitors and TNF blockers.

There is concern on an increased risk for venous thromboembolism for all agents in the JAK class. This is considered possible to handle through information in the SmPC.

There is currently limited long-term data on the safety profile of filgotinib. Up to current cut-off, the exposure-adjusted incidence rate of death is higher for filgotinib 200 mg than for the comparator adalimumab, although the actual numbers are small. The relevance of this observation is difficult to assess taken into account that overall the differences between all the analyzed treatment groups are small with overlapping 95% CIs and that there are no dose-dependency observed for the most important AESIs of serious infections, MACE or malignancy. The CHMP considered that those uncertainties would need to be followed-up post approval but were sufficiently addressed in the SmPC and the RMP.

Regarding safety in fragile populations, there is very limited experience from the use of filgotinib in patients over 75 years of age. In the available data, an increased risk for serious AEs is observed for the 200 mg compared to the 100 mg dose. Therefore, a starting dose of 100 mg is recommended to patients aged 75 or above.

In patients with moderate renal impairment, a 1.96-fold increase of AUCeff is observed. Therefore, a dose of 100 mg is recommended to patients with moderate and severe renal impairment.

JAK inhibitors are known to be teratogenic, and filgotinib is contraindicated during pregnancy.

There is concern on the clinical consequences of non-clinical findings on substantial decrease of fertility, impaired spermatogenesis and histopathological effects on male reproductive organs. These unexpected findings were observed already from 4 weeks of treatment and with low marginals and only partial recovery. The clinical consequences of these findings are currently uncertain and are being investigated in ongoing studies in human males (MANTA [Study GS-US-418-4279] and MANTA-RAy [Study GLPG0634-CL-227]). At the CHMP's request, the applicant has included warnings in the SmPC section 4.4, the PL and in the educational material regarding the risk for infertility in male patients treated with filgotinib, aiming to limit the use of filgotinib to female patients and male patients without intent of fathering a child. This was considered acceptable to the CHMP until the results of the MANTA studies are available (1st half 2021).

3.7.2. Balance of benefits and risks

Favourable effects in terms of overall clinical response (as measured by ACR 20) achieving disease target state (as measured by the proportion of subjects reaching low disease activity and remission) and prevention of structural damage have been demonstrated across the populations targeted by the proposed indication. Both short term and long-term favourable effects i.e. maintenance of effect have been shown.

The CHMP questioned the initially proposed indication "*[Tradename] is indicated as monotherapy for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have highly active and early progressive (erosive) disease, were not previously treated with MTX, and for whom treatment with MTX is inappropriate"* in the D120 LoQ in the light of the data submitted with this application, the totality of data on JAK-inhibitors that has so far become available and also considering that such indication would have been the 1st in the class. The first line indication was withdrawn by the applicant with their responses to the D120 LoQ.

In addition, filgotinib was initially proposed to be given either in monotherapy or in combination with MTX or other csDMARDs. Since data supporting the combination with csDMARDs other then MTX were not presented, this was raised as a major objection in the D120 LoQ. As a consequence, the proposal for use in combination with csDMARDs was withdrawn by the applicant with their responses to the D120 LoQ.

The degree of support for monotherapy in DMARD-IR subjects is considered sufficient as it includes both observed data from DARWIN 2 and extrapolation from FINCH 3. Extrapolation from the first-line FINCH 3

study is considered justified on the basis of filgotinib in combination therapy generally displaying efficacy across the treatment lines.

The major safety concern given the immunosuppressive effect of filgotinib is the risk for infections. The most commonly reported infections were mild (for example upper respiratory tract infections, nasopharyngitis and urinary tract infection), although also severe infections and deaths due to infections occurred. Filgotinib is contraindicated in active serious infections and active TB. Adequate warnings are included in Section 4.4 of the SmPC.

The clinical consequences of non-clinical findings on substantial decrease of fertility, impaired spermatogenesis and histopathological effects on male reproductive organs are unknown. The clinical consequences of these findings are being investigated in ongoing studies in human males (MANTA [Study GS-US-418-4279] and MANTA-RAy [Study GLPG0634-CL-227]). At the CHMP's request, the applicant has included warnings in the SmPC section 4.4, the PL and in the educational material regarding the risk for infertility in male patients treated with filgotinib, aiming to limit the use of filgotinib to female patients and male patients without intent of fathering a child. This was considered acceptable to the CHMP until the results of the MANTA studies are available (1H21).

3.8. Conclusions

The overall B/R of Jyseleca is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Jyseleca is favourable in the following indication:

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).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports 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 shall submit the first periodic safety update report for this product within 6 months following authorisation.

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), potential effect on male fertility, venous thromboembolisms (VTEs), and major cardiovascular events (MACE) 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 impaired spermatogenesis, leading to possible reduction in male fertility
  - Information on the potential risk of impaired spermatogenesis with filgotinib treatment, based on the available data
  - Language to discuss with male patients their plans to father a child, noting the potential for reduction in sperm count with filgotinib treatment, and the possible impact on fertility
- 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
- 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
  - Information on the risk of an increase in lipid parameters including dose-dependent increases in total cholesterol, and high-density lipoprotein
- Prescribing in the very elderly (75 years and above)
  - Information on the treatment of patients aged 75 years and above with filgotinib
  - Guidance on the dose of filgotinib to be used in patients aged 75 years and above
- 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 on the possible effect on male fertility
- Information about monitoring cholesterol levels during treatment.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that filgotinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.