16 September 2021
EMA/553754/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jyseleca

International non-proprietary name: filgotinib

Procedure No. EMEA/H/C/005113/II/0001

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AEIs	adverse events of interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	Adult Treatment Panel
AUC_{eff}	weighted sum of steady-state AUC_{tau} values of filgotinib and GS-829845 based on their relative potencies on JAK1 inhibition and differences in molecular weight
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BfArM	Bundesinstitut fur Arzneimittel und Medizinprodukte
CD	Crohn's disease
C_{eff}	weighted sum of steady-state C_{tau} values of filgotinib and GS-829845 based on their relative potencies on JAK1 inhibition and differences in molecular weight
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CK	creatine kinase
C_{max}	maximum observed concentration of drug
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
Diff	difference
EAER	exposure-adjusted event rate
EAIR	exposure-adjusted incidence rate
EBS	endoscopy/bleeding/stool frequency
EQ-5D	EuroQoL (5 dimensions)
EQ-VAS	EuroQol visual analogue scale
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIL	filgotinib
GEE	generalized estimating equation
GI	gastrointestinal
Gilead	Gilead Sciences
HDL	high-density lipoprotein
HRQoL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IL	interleukin
JAK	Janus kinase
LDL	low-density lipoprotein

LOCF	last-observation-carried-forward
LTE	long-term extension
Maint	maintenance
MCS	Mayo Clinic Score
MHRA	Medicines and Healthcare products Regulatory Agency
NEst	not estimable
NMSC	nonmelanoma skin cancer
PCS	Physical Component Summary
PE	pulmonary embolism
PK	pharmacokinetic(s)
PT	preferred term
PY	person-years
PYE	patient-years of exposure
QD	once daily
RA	rheumatoid arthritis
RB	rectal bleeding
SAE	serious adverse event
SF	stool frequency
SF-36	36-Item Short Form Survey
SOC	system organ class
STAT	signal transducer and activator of transcription
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences Ireland UC submitted to the European Medicines Agency on 12 October 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the treatment of active ulcerative colitis in adult patients for Jyseleca. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated accordingly. Version 1.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to do minor updates to the Annex II and to implement minor editorial changes in the SmPC and Package Leaflet.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0386/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0371/2018 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 MAH 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.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

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

Timetable	Actual dates
Submission date	12 October 2020
Start of procedure:	31 October 2020
CHMP Co-Rapporteur Assessment Report	22 December 2020
CHMP Rapporteur Assessment Report	22 December 2020
PRAC Rapporteur Assessment Report	4 January 2021
PRAC members comments	6 January 2021
Updated PRAC Rapporteur Assessment Report	11 January 2021
PRAC Outcome	14 January 2021
CHMP members comments	18 January 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 January 2021
Request for supplementary information (RSI)	28 January 2021
CHMP Rapporteur Assessment Report	20 April 2021
PRAC Rapporteur Assessment Report	24 April 2021
PRAC members comments	28 April 2021
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	06 May 2021
CHMP members comments	10 May 2021
Updated CHMP Rapporteur Assessment Report	12 May 2021
2nd Request for supplementary information	20 May 2021
CHMP Rapporteur Assessment Report	17 August 2021
PRAC Rapporteur Assessment Report	20 August 2021
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	02 September 2021
CHMP members comments	06 September 2021
Updated CHMP Rapporteur Assessment Report	10 September 2021
Opinion	16 September 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The following indication is claimed in this extension of indication procedure: "*Jyseleca is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent*."

Epidemiology

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disease that affects the colon, most commonly afflicting adults aged 30 to 40 years and resulting in disability. It is characterized by relapsing and remitting mucosal inflammation, starting in the rectum and extending to proximal segments of the colon. From the turn of the 21st century, UC has become a global disease with accelerating incidence in newly industrialized countries. Although the incidence is stabilizing in Western countries, burden remains high, as prevalence exceeds 0.3%. These data highlight the need for research into the prevention of UC and innovations in health care systems to manage this complex and costly disease (Ng 2017).

Aetiology and pathogenesis

The pathogenesis of UC is multifactorial and comprises immune, genetic, environmental, and microbial components.

Clinical presentation

Dis-coordinated activity of both innate and adaptive immune responses, in combination with epithelial barrier defects and dysbiosis, leads to an inflammatory cascade, resulting in clinical signs and symptoms of UC (Ungaro 2016). Hallmark symptoms of UC are bloody diarrhea, rectal urgency, and tenesmus. The clinical course usually involves periods of remission interspersed with periods of active disease. Ulcerative colitis may also be associated with extraintestinal manifestations, including ocular lesions, skin lesions, arthritis, and primary sclerosing cholangitis. In addition, UC carries an increased risk of colorectal cancer.

Management

The treatment paradigm for UC has historically comprised an initial treatment for acute disease, with the goal of inducing a state of clinical remission, followed by a therapeutic intervention to maintain remission. Generally, patients presenting with mild to moderate disease activity are initially administered an anti-inflammatory agent such as a 5-aminosalicylate (5-ASA) derivative, with or without concurrent corticosteroids. Patients who fail to respond to initial therapy or who present with

moderate to severe disease activity require treatment with more effective agents such as immunomodulators and biologic therapy. For nearly 2 decades, biological therapies were dominated by anti-tumor necrosis factor (TNF)-α agents but have recently included anti-integrin and anti–interleukin (IL)-12/IL-23 antibodies (Sands 2019b, Singh 2018). Although biological therapies have led to substantial improvements in the care of patients with UC and have become an integral part of standard therapy, not all treated patients benefit from these therapies (Colombel 2010, Feagan 2013). Depending on the duration of therapy and the clinical endpoints chosen, approximately one-third of patients do not respond after initiation of biological therapy (primary nonresponse). Among patients who initially respond to treatment with biologics, 30% to 50% eventually stop responding (secondary nonresponse), resulting in exposure to potential side effects and toxicities without durable clinical benefit. These findings highlight the unmet medical need in these patients. The clinical need for new therapies has led to the development of orally bioavailable small-molecule inhibitors that target signal transduction pathways involved in the pathogenesis of UC, including Janus kinase (JAK) inhibitors. Janus kinases are cytoplasmic protein tyrosine kinases that transduce cytokine signaling from membrane receptors to signal transducer and activator of transcription (STAT) factors. The 4 known JAK family members are JAK1, JAK2, JAK3, and TYK2. Upon cytokine binding, JAKs autophosphorylate or transphosphorylate, creating sites for STAT binding and subsequent phosphorylation, dimerization, and translocation to the nucleus where STATs modulate the transcription of effector genes. Currently, the only JAK inhibitor approved for the treatment of UC is tofacitinib.

2.1.2. About the product

Filgotinib (FIL; GS-6034, formerly GLPG0634) is an adenosine triphosphate (ATP) competitive and reversible inhibitor of the JAK family. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor receptor interactions on the cellular membrane. JAK1 is important in mediating inflammatory cytokine signals, JAK2 in mediating myelopoiesis and erythropoiesis and JAK3 plays critical roles in immune homeostasis and lymphopoiesis. Within the signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity including gene expression. Filgotinib modulates these signalling pathways by preventing the phosphorylation and activation of STATs. In biochemical assays, filgotinib preferentially inhibited the activity of JAK1 and showed > 5 fold higher potency of filgotinib for JAK1 over JAK2, JAK3 and TYK2. In human cellular assays, filgotinib preferentially inhibited JAK1/JAK3 mediated signalling downstream of the heterodimeric cytokine receptors for interleukin (IL) 2, IL 4 and IL 15, JAK1/2 mediated IL 6, and JAK1/TYK2 mediated type I interferons, with functional selectivity over cytokine receptors that signal via pairs of JAK2 or JAK2/TYK2. GS-829845, the primary metabolite of filgotinib, was approximately 10 fold less active than filgotinib in *in vitro* assays, while exhibiting a similar JAK1 preferential inhibitory activity. In an *in vivo* rat model, the overall pharmacodynamic effect was predominantly driven by the metabolite.

It is currently indicated in 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 pivotal Study GS-US-418-3898 was a randomized, double-blind, placebo-controlled combined Phase2b/3 study in adult subjects with moderately to severely active UC who were biologic naive or biologic experienced. Filgotinib and placebo were administered orally for up to 58 weeks. This study was designed to evaluate the efficacy and safety of filgotinib in the induction and maintenance of remission of UC.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No scientific advice has been sought from the CHMP.

2.2. Non-clinical aspects

2.2.1. Introduction

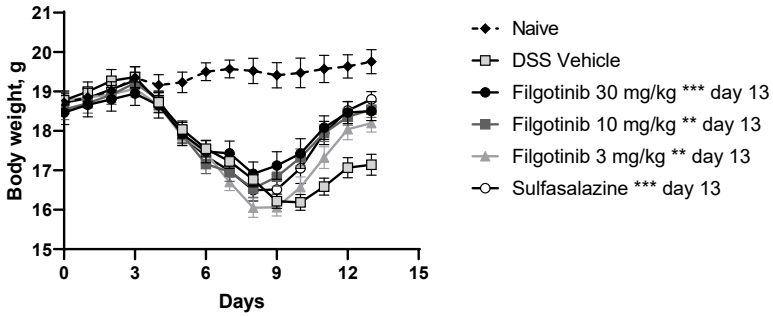
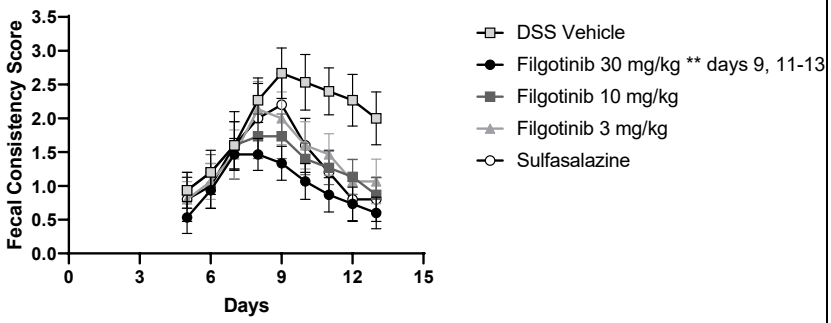
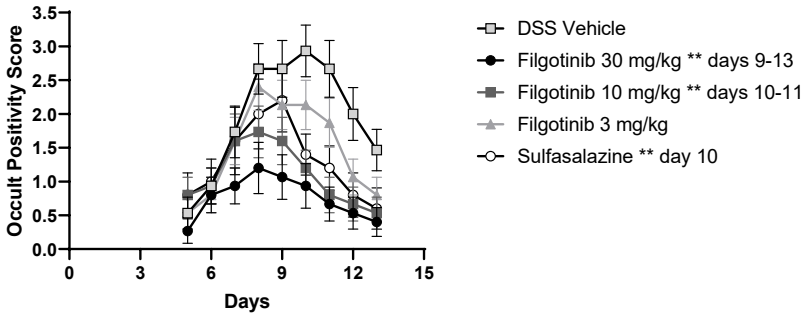
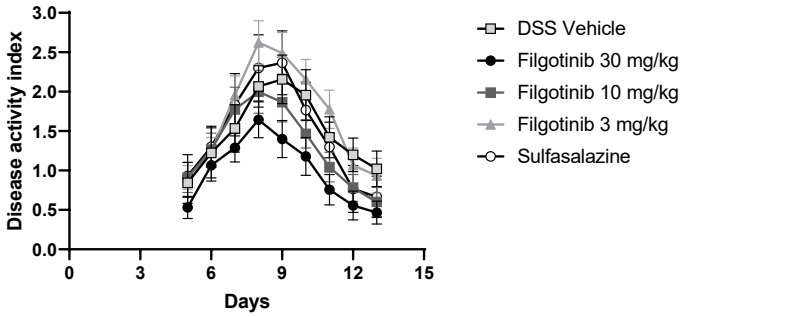
A comprehensive package of non-clinical pharmacology, pharmacokinetic, and toxicology data for filgotinib was submitted as part of the original marketing application (MAA) (EMA/CHMP/367247/2020) for the treatment of rheumatoid arthritis (RA). New pharmacology data has been generated to support the extension of the indication to include the treatment of UC.

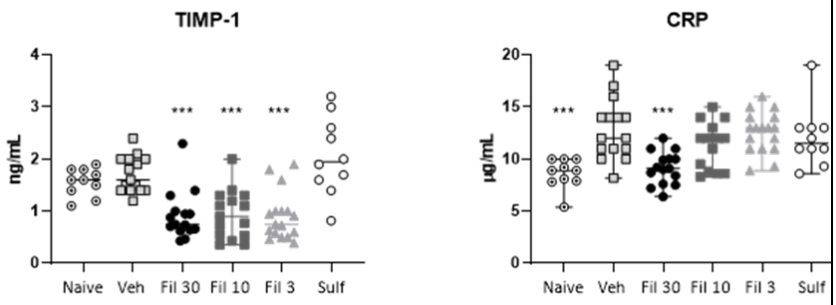
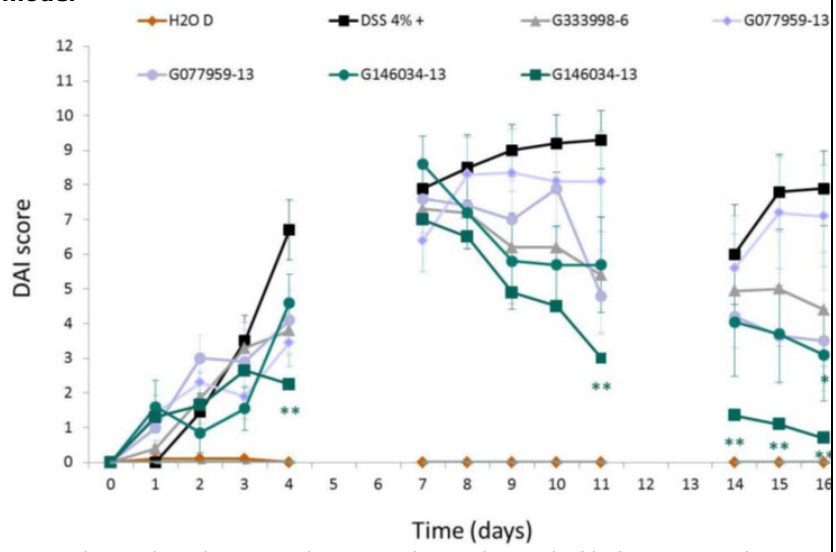
2.2.2. Pharmacology

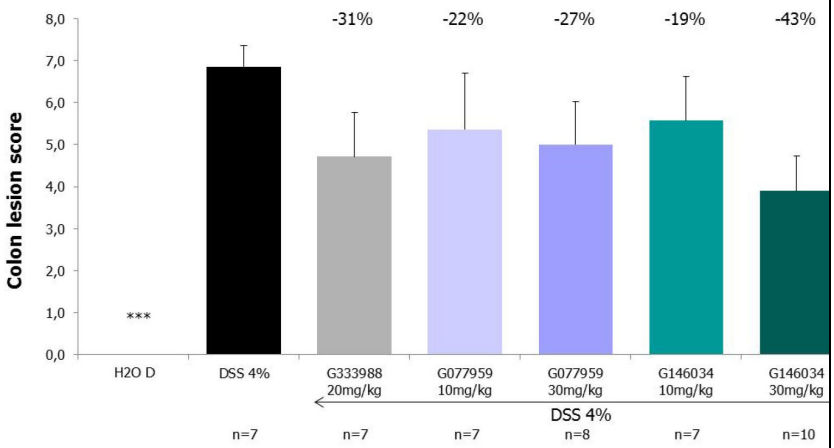
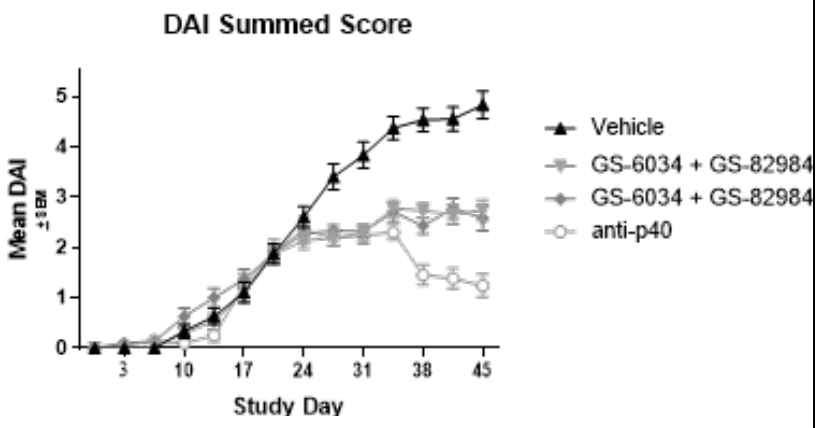
The MAH has evaluated the effect of filgotinib and its metabolite, GS-829845, in three intestinal inflammation models of human UC in mice: the acute DSS model, the chronic DSS model and the T cell transfer model. While these animal models cannot recapitulate all aspects of human UC, DSS models and T cell transfer models are commonly suited to screen for substances that affect the innate immune system and the adaptive immune system, respectively. The new *in vivo* studies with filgotinib are presented in the table below.

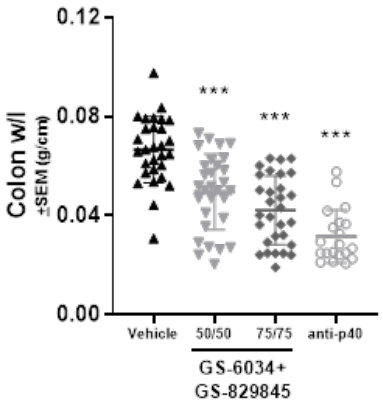
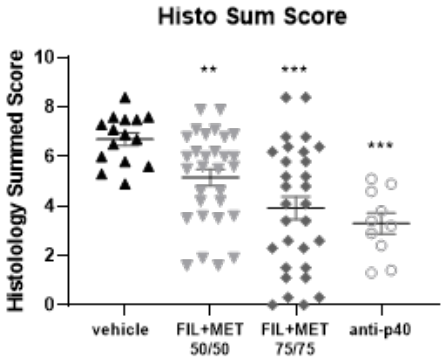
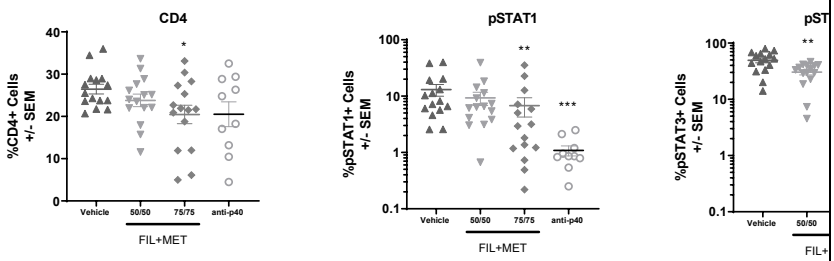
Table 1 In vivo studies with filgotinib in models of intestinal inflammation in mice

Study	Test system	Objectives and Results
In vivo Acute DSS model of intestinal inflammation PC-296-2052 (INV-S160176) non-GLP	Female mouse/C57BL/6 0, 3, 10, 30 mg/kg, qd, PO, N=15/group Positive control: sulfasalazine at 0.5 mg/kg per day, PO <u>Colitis model:</u> 4% DSS in drinking water ad libitum for 7 days followed by filtered water for another 7 days to induce colitis. Dosing started on Day 5 of DSS treatment and dosing continued until necropsy on Day 14. <u>Endpoints:</u> Efficacy was assessed by the disease activity index (DAI) as measured by body weight, fecal consistency and occult positivity	**Objective:** Evaluation of filgotinib in the acute DSS model of intestinal inflammation **Results:** **Filgotinib improved body weight, fecal consistency and occult positivity in acute DSS model**

	(bleeding). Additional measures of efficacy included colon weight per length (w/l) ratios and colon histopathology. Inflammatory proteins (CRP, TIMP1) and whole blood IL-6-stimulated phospho-STAT1 in CD4+ T cells were also measured.	**Body Weight**  **Fecal Consistency**  **Occult Positivity**  **DAI**  Asterisks indicate that the treatment is significantly different from the vehicle control. Significance levels: ***< 0.001, **< 0.01, * < 0.05 (Wilcoxon rank sum test)

		Filgotinib Reduced Serum Inflammatory Protein Levels in the Acute DSS Model  Asterisks indicate that the treatment is significantly different from the vehicle control. Fil 30, Fil 10, and Fil 3 indicate filgotinib doses in mg/kg. Significance level: ***<0.001 <u>PK analysis</u> Filgotinib plasma exposure was above the mouse whole blood EC50 value of 3.1 µM (IL-6 stimulated pSTAT1 in CD4+ T cells) for approximately 2 hours in the 30 mg/kg group, and GS-829845 was below the mouse whole blood EC50 value of 19.9 µM for the full dosing period. The maximum inhibition of whole blood IL-6-stimulated phosphor STAT1 in CD4+ T cells of 45%±10 was observed in the 30 mg/kg group at 0.5 hours post-last dose. <u>CHMP conclusion:</u> In the acute DSS model in mice, filgotinib dose-dependently improved DSS-induced acute colitis-associated disease activity, reduced some histological measures of colonic inflammation, and reduced inflammatory serum proteins. Most effects of filgotinib at 30 mg/kg in this model appeared to be comparable to the positive control sulfasalazine.
In vivo Chronic DSS model 000456 (GLPG0634 1431) non-GLP	Female mouse/BALB/c 0, 10, 30 mg/kg/day, qd, PO, N=10/group Reference compounds: Tofacitinib G077959 10, 30 mg/kg, qd, PO Sulfasalazine G333998 20 mg/kg, qd, PO <u>Colitis model</u> 4% DSS in drinking water for 4 days followed by regular drinking water for 3 days, and this DSS cycle was repeated until Day 18 when the animals were euthanized (000456). Dosing of groups of 10 mice began on Day 1 when DSS treatment was initiated. <u>Endpoints</u> Efficacy was assessed by the	**Objective**: Evaluation of filgotinib activity in the chronic DSS induced colitis model **Results**: **Filgotinib improved disease activity index scores in chronic DSS model**  Orange diamonds and H2O D indicate non-diseased animals, black squares and DSS 4% indicate vehicle treated animals, gray triangles and G333998-6 indicate animals dosed with sulfasalazine at 20 mg/kg, purple diamonds and G077959-13 indicate animals dosed with tofacitinib at 10 mg/kg, purple circles and G077959-13 indicate animals dosed with tofacitinib at 30 mg/kg, green circles and G146034-13 indicate animals dosed with filgotinib at 10 mg/kg, green squares and G146034 indicate animals dosed with filgotinib at 30 mg/kg. Asterisks indicate that the treatment is significantly different from the vehicle control. Significance levels: *< 0.05, **< 0.01

	disease activity index (DAI) as measured by body weight, fecal consistency and occult positivity (bleeding). Additional measures of efficacy included histological colon lesion scoring which included severity of inflammation, thickness of inflammation, epithelial damage, and extent of lesions. serum levels of inflammatory proteins were also measured.	**Filgotinib showed a trend to improve Colon Lesion Scores**  PK analysis Plasma exposures of filgotinib and GS-829845 did not exceed mouse whole blood EC50 values at steady state in this model (IL-6-stimulated pSTAT1 in CD4+ T cells), calculated as 1600 ng/mL and 7100 ng/mL, respectively. CHMP conclusion: Filgotinib 30 mg/kg significantly reduced DAI score on Days 4, 11, 14, 15, and 16 in the chronic DSS model. A trend in colon lesion score reduction by 43% was observed with filgotinib 30 mg/kg.The plasma exposure of filgotinib was estimated to be lower than EC50 in mouse whole blood assay over the entire dosing interval. Tofacitinib and sulfasalazine had no significant effect on the DAI score in this study.
In vivo T cell transfer model of colitis PC-418-2002 (MCD4 GLD 9) Non-GLP	Female Mouse/ C.B-17 SCID Treatments: Filgotinib was co-dosed orally once daily with GS-829845 at 50/50 mg/kg/day or 75/75 mg/kg/day Vehicle, PO once daily Anti-p40 (anti IL-12/23) IP once weekly as a reference positive control. N=30/group Model: Naïve BALB/c mice were euthanized, spleens were collected and CD4+CD45RBhi cells were isolated and IP-injected into	**Objective:** Evaluation of filgotinib co-dosed with its metabolite in a T cell transfer model of colitis. **Results** **Filgotinib and GS-829845 Improved Disease Activity Index, Colon Weight Per Length and Histology Inflammation Measures** 

	female SCID mice to induce colitis (PC-418-2002). Twenty two days later, dosing was initiated in groups of 30 animals when disease was apparent. <u>Endpoints:</u> Efficacy was assessed by the disease activity index (DAI summed score) as measured by body weight, fecal consistency and occult positivity (bleeding). Additional measures of efficacy included colon weight per length (w/l) ratios and colon histopathology measures of gland loss, erosions, mucosal thickness, hyperplasia, polymorphonuclear leukocyte cell (PMN) percent, neutrophil scoring, edema.	  DAI summed score top; Colon w/l ratio left; Histopathology summed score right. 50/50 and 75/75 indicate doses of filgotinib and GS-829845 in mg/kg. Significance levels: *** p< 0.005, ** p< 0.01 **Filgotinib and GS-829845 Reduced pSTAT1+ and pSTAT3+ in Colons**  50/50 and 75/75 indicate doses of filgotinib and GS-829845 in mg/kg. Significance levels: ** p< 0.01, *** p< 0.005 <u>PK analysis</u> Plasma exposures of filgotinib and GS-829845 were similar between the two dosing groups. Filgotinib and GS-829845, respectively, were above mouse whole blood EC50 values (IL 6_stimulated pSTAT1 in CD4+ T cells) in both dosing groups for approximately 4 and 6 hours. <u>CHMP conclusion:</u> Filgotinib co-dosed with its metabolite was efficacious in the mouse adoptive T cell transfer model of intestinal inflammation showing significant effects on disease activity by measures of inflammation and on numerous PD markers.

DAI, Disease Activity Index; DSS, Dextran Sodium Sulfate; pSTAT, phosphorylated signal transducer and activator of transcription proteins; w/l, weight per length of colon.

2.2.3. Pharmacokinetics

No new pharmacokinetics data were provided. This was considered acceptable by the CHMP.

2.2.4. Toxicology

No new toxicology data were submitted. In the initial marketing authorisation application, 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 animals including 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.

At LOAEL for male reproductive organs generally no changes of hormonal levels or seminology parameters was observed except for increased LH levels in rats. At higher doses (and exposure) a decrease of testosterone, 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 in which partial reversibility of findings in testes (minimal to moderate) and epididymides (minimal to severe) was observed after 8 weeks of recovery when dosed at 60 mg/kg/day (only high dose animals were included during the recovery period). Further, partial reversibility was observed in dogs treated for 13 weeks with the high dose of filgotinib (15 mg/kg/day) followed by 8 weeks of recovery showing reduced number of sperms and normal sperms without microscopic testicular changes.

2.2.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) was previously submitted for Jyseleca (filgotinib) as part of the EU initial MAA. The initial ERA for filgotinib predicted environmental concentrations were estimated based on forecasted sales figures provided by the MAH. These forecasts covered the period of 2020 – 2028 for filgotinib and included predicted consumptions for future indications to be filed for filgotinib. Therefore, the MAH stated that it can be considered that the sales forecasts employed in the previous ERA accounted for the potential sales increase due to the proposed addition of the ulcerative colitis indication. The CHMP agreed with the MAH that the estimated predicted environmental concentrations (PECs) are still conservative and that no further update to the assessment is necessary.

The ERA for filgotinb is summarised below.

Table 2 Summary of main ERA 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	<u>Soil</u> 1. K_{oc} 24384 2. K_{oc} 266815 3. K_{oc} 83378 <u>Sludge</u> 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*

In summary, 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. Based on a complete Phase II assessment it can be concluded that filgotinib is not expected to pose a risk to the environment.

2.2.6. Discussion on non-clinical aspects

A series of *in vivo* pharmacodynamic studies were conducted in order to characterize the efficacy of filgotinib and the major metabolite GS-829845 in animal models of intestinal inflammation.

In innate and adaptive immune cell-driven UC models of intestinal inflammation, filgotinib dosed alone or in combination with its metabolite GS-829845, showed improvements of body weight, fecal

consistency and bleeding with a reduction in colonic histological measures of inflammation, a reduction in colonic pSTAT1 and pSTAT3 levels, a reduction in colonic inflammatory gene expression and tissue cytokines, immune cell subset homeostatic restoration, and a reduction in serum inflammatory proteins.

Consistent with a longer duration of filgotinib exposure, the improvements in disease activity and pharmacodynamic effects were more pronounced in the T cell transfer model compared to the DSS models.

Overall, the results from the provided *in vivo* pharmacodynamic studies provide supportive scientific rationale for filgotinib as a treatment in patients with UC.

The toxicological program provided at the initial MAA, 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 (see Clinical Safety section).

Furthermore, a mistake from the initial marketing authorisation in 5.3 of the SmPC was corrected and it is now stated that spermatogenic and histopathological effects were not fully reversible at exposure margins of approximately 7- to 9-fold the exposure at the 200 mg once daily dose in humans. This information is based on studies GLPG0634-TX-012 and GLPG0634-TX-024 according to which histopathological effects in the testes were no longer present in 15 mg/kg/day animals, while in rats complete recovery was demonstrated after 5 weeks recovery at 30 mg/kg in the fertility study (GLPG0634-TX-024).

The new indication is not likely to lead to a significant increase in environmental exposure further to the use of filgotinib. Filgotinib is not expected to pose a risk to the environment, since the calculated risk quotients were all below 1.

2.2.7. Conclusion on the non-clinical aspects

A comprehensive package of non-clinical pharmacology, pharmacokinetic, and toxicology data for filgotinib has been assessed as part of the initial MAA (EMA/CHMP/367247/2020) for the treatment of rheumatoid arthritis (RA).

New pharmacology data has been generated to support the extension of the indication to include the treatment of UC. Those results provide supportive scientific rationale for filgotinib as a treatment in patients with UC.

The new indication is not likely to lead to a significant increase in environmental exposure further to the use of filgotinib. Filgotinib is not expected to pose a risk to the environment, since the calculated risk quotients were all below 1.

Overall, the CHMP considered that the non-clinical package to support the new indication in UC was acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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

Study Number	Treatment Regimens	Subject Population	No. of Subjects Who Received Study Drug	Region
Phase 2b/3 Studies				
GS-US-418-3898 (SELECTION)	Cohort A Induction Study[a] 2:2:1 ratio to filgotinib 200 mg, filgotinib 100 mg, or placebo QD Cohort B Induction Study[a] 2:2:1 ratio to filgotinib 200 mg, filgotinib 100 mg, or placebo QD Maintenance Study Subjects who received filgotinib in the induction studies were randomized 2:1 to either continue on the assigned filgotinib regimen or switch to placebo. Subjects who received placebo in the induction studies continued on placebo.	Cohort A Induction Study Biologic naive Cohort B Induction Study Biologic experienced Maintenance Study Biologic naive and biologic experienced	Cohort A Induction Study 659 total: 245 filgotinib 200 mg; 277 filgotinib 100 mg; 137 placebo Cohort B Induction Study 689 total: 262 filgotinib 200 mg; 285 filgotinib 100 mg; 142 placebo Maintenance Study 664 total: 202 filgotinib 200 mg; 179 filgotinib 100 mg; 283 placebo	Asia, Australia, Eastern and Western Europe, New Zealand, South Africa, and Central, North, and South America
Phase 3 LTE Study				
GS-US-418-3899 (SELECTION LTE)	Filgotinib 200 mg, filgotinib 100 mg, or placebo	Biologic-naive and biologic-experienced subjects who completed or met protocol-specified efficacy discontinuation criteria in Study GS-US-418-3898	1161 total: 871 filgotinib 200 mg; 157 filgotinib 100 mg; 133 placebo	Asia, Australia, Eastern and Western Europe, New Zealand, South Africa, and Central, North, and South America

CSR = clinical study report; LTE = long-term extension; QD = once daily; TNF = tumor necrosis factor; US = United States
a US and Korea males who were not dual refractory (having failed any TNF-α antagonist and vedolizumab) were randomized 2:1 to either filgotinib 100 mg or placebo.
Source: m2.7.3, Table 1; GS-US-418-3898 Final; and GS-US-418-3899 Interim

2.3.2. Pharmacokinetics

The pharmacokinetics of filgotinib in the UC patient population was studied in study GS-US-418-3898. A tabular summary of the study design, treatment regimens, and subject populations is provided in the table below.

Table 3 Tabular Summary of Clinical Pharmacology Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-418-3898 (SELECTION)	Cohort A Induction Study: To evaluate the efficacy of filgotinib as compared with placebo in establishing endoscopy/bleeding/stool frequency (EBS) remission at Week 10 Cohort B Induction Study: To evaluate the efficacy of filgotinib as compared with placebo in establishing EBS remission at Week 10 Maintenance Study: To evaluate the efficacy of filgotinib as compared with placebo in establishing EBS remission at Week 58	Combined Phase 2b/3, double-blind, randomized, placebo-controlled studies	Induction studies[a]: Subjects were randomized 2:2:1 as follows: • Filgotinib 200 mg group: Filgotinib 200 mg (1 × 200-mg tablet and 1 × PTM 100-mg tablet) QD • Filgotinib 100 mg group: Filgotinib 100 mg (1 × 100-mg tablet and 1 × PTM 200-mg tablet) QD • Placebo control group: PTM filgotinib 200 mg and PTM filgotinib 100 mg, QD Maintenance Study: Subjects who received filgotinib in the induction studies were rerandomized 2:1 at Week 11 to continue on the assigned filgotinib regimen or switch to placebo. Subjects who received placebo in the induction studies remained on placebo. At completion of the Week 58 dosing period, subjects who had not discontinued assigned study treatment were provided the option to enroll into a separate LTE study (GS-US-418-3899)	Induction studies: 11 weeks Maintenance Study: 47 weeks	Cohort A Induction Study: Randomized: 660 subjects Treated: 659 subjects Completed study: 618 subjects Cohort B Induction Study: Randomized: 691 subjects Treated: 689 subjects Completed study: 623 subjects Maintenance Study: Randomized: 664 subjects Treated: 664 subjects Completed study: 401 subjects	Cohort A Induction Study: Biologic-naive subjects with moderately to severely active ulcerative colitis (UC) Cohort B Induction Study: Biologic-experienced subjects with moderately to severely active UC Maintenance Study: Subjects who completed the induction study and achieved either EBS remission or Mayo Clinic Score response at Week 10	Study completed; Final CSR

CSR = clinical study report; EBS = endoscopy/bleeding/stool frequency; LTE = long-term extension; PTM = placebo to match; QD = once daily; TNF = tumor necrosis factor; UC = ulcerative colitis; US = United States

a Male subjects from the US and Korea who had not failed at least 2 biologic therapies (any TNF-α antagonist and vedolizumab; non-dual refractory) were randomized in a 2:1 ratio to either filgotinib 100 mg or respective placebo QD.

Methods

Bioanalytical methods

The bioanalytical method for the determination of filgotinib and GS-829845 (primary metabolite of filgotinib) in human plasma with dipotassium ethylenediaminetetraacetic acid (K2EDTA) as anticoagulant was developed and validated at QPS, LLC (Newark, DE, United States). The method involved protein precipitation of filgotinib and GS-829845 and their deuterated internal standards (GS 833369 and GS-833368, respectively) from human plasma, followed by liquid chromatography-tandem mass spectrometry (LC MS/MS). Bioanalytical method validation parameters are summarized in the table below.

Table 4 Bioanalytical Method Validation Parameters for Determination of Filgotinib and GS-829845 in Human Plasma (QPS 60-1613)

	Filgotinib	GS-829845
Calibrated Range (ng/mL)	1-2000	2-4000
Interassay Precision (%CV)	≤ 5.6	≤ 4.7
Interassay Accuracy Range (%RE)	1.9-9.7	1.6-8.7
Studies Supported	GS-US-418-3898	

CV = coefficient of variation; RE = relative error
GS-829845: primary metabolite of filgotinib

Population Pharmacokinetic Analysis

A population PK analysis of filgotinib (GS-6034) and GS-829845 in subjects with UC was performed with the objectives of:

- Estimate typical values and interindividual variability (IIV) of PK parameters in this population
- To evaluate the effects of UC disease-related covariates on the PK of filgotinib and GS-829845 to better understand clinical factors that might affect exposure in individual subjects
- To provide model predicted individual subject PK parameter estimates from PopPK models for exposure-response (ER) analysis

PopPK analyses of filgotinib and GS-829845 evaluated data from a Phase 2b/3 clinical study in subjects with UC (GS-US-418-3898). The table below provides further details regarding study drug regimens and the number of subjects with intensive or sparse PK sampling. Subjects were evaluable for PopPK analysis if they had at least 1 adequately documented filgotinib administration and a corresponding measurable plasma concentration after administration of the dose.

Table 5 GS-US-418-3898 - study drug regimens and the number of subjects with intensive or sparse PK sampling

Study Number	Dosage Regimen	Number of Subjects			
		Intensive Sampling		Sparse Sampling	
		FIL	GS-829845	FIL	GS-829845
GS-US-418-3898	100 or 200 mg QD for 11 weeks (induction) or 47 weeks (maintenance)	41	41	1001	1010

FIL = filgotinib; QD = once daily

Filgotinib is extensively metabolized primarily via carboxylesterase 2, and GS-829845 is the major circulating active metabolite, accounting for 92% of the circulating total radioactivity in plasma. Clinical and non-clinical data indicate that renal elimination is the primary clearance pathway for GS-829845.

The PK was similar between subjects with UC and subjects with rheumatoid arthritis (RA) for both filgotinib and GS-829845, based on comparison of intensive PK from Phase 3 studies. Thus, the current models for filgotinib and GS-829845 in subjects with UC were based on previously developed models to characterize PK in subjects with RA and healthy subjects. External model validation was first applied to assess model adequacy. Parameter re-estimation based on the same structural models would be further performed if improvement in model fitting was needed to better describe the PK profiles in subjects with UC.

The PopPK analysis was performed using the computer program NONMEM (ICON; Gaithersburg, MD) Version 7.4 or later, Perl-speaks-NONMEM Version 4.8.1 or later, and R Version 3.6.3 or later.

Filgotinib Model

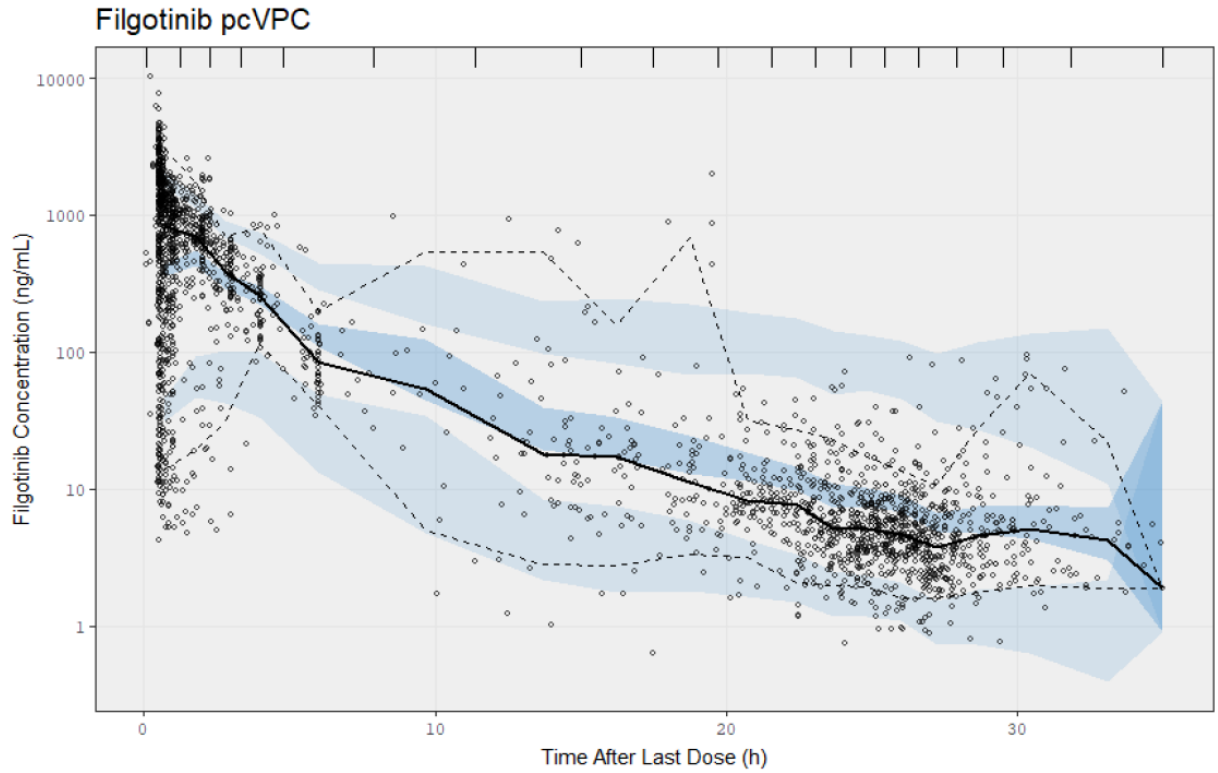
The Original Dataset contained 2759 filgotinib concentration-time data points from 1020 subjects. The Model Evaluation Dataset included all PK data except the BLQ samples (6%, 159 PK samples). In the Model Development Dataset, 239 samples (9%) of the filgotinib plasma concentrations were further censored based on pre-specified criteria (pre-dose samples and late PK samples etc). The remaining data in the Model Development Dataset had a total of 2361 data points from 1001 subjects. A summary of the filgotinib PopPK Analysis datasets is presented in the table below.

Table 6 Summary of Filgotinib Concentration in the Population Pharmacokinetic Analysis Datasets in Study GS-US-418-3898

Analyte	Original Dataset		Model Evaluation Dataset		Model Development Dataset	
	Number of Subjects	Data Points	Number of Subjects	Data Points	Number of Subjects	Data Points
Filgotinib	1020	2759	1020	2600	1001	2361

Source: Ad Hoc PopPK Table 10601.1

The final filgotinib model was based on a previously developed model for subjects with RA and healthy subjects. The external validation indicated that the RA model systematically underpredicted Cmax and overpredicted Ctau of filgotinib in subjects with UC (Figure 1). As such, the model parameters were re-estimated and RA-related covariates adjusted.



pcVPC = prediction-corrected visual predictive check
pcVPC plots show the median (solid line) and spread (5th to 95th percentile, dashed lines) of the observed concentrations in all subjects. The darker blue area is the 95% CI of the simulated median, and the lighter blue area is the 95% CI of the simulated 5th and 95th percentiles. Open circles show the observed data.

Figure 1 Filgotinib pcVPC Using External Validation

The final filgotinib population PK model based on data from UC subjects compriced of a 2-compartment model included a mixture model for absorption and linear elimination. An IIV was included on oral clearance (CL/F), apparent central volume of distribution of the drug (V_c/F), k_a, and duration of the zero-order input (D1). Previously identified significant covariates were retained in the model, including formulation on relative bioavailability (F); baseline body weight (WT) on CL/F, apparent intercompartmental clearance (Q/F), V_c/F, and apparent peripheral volume of distribution (V_p/F); sex female (SEXF) on CL/F; and race (white and Asian versus black or African American versus other) on V_c/F. Baseline C-reactive protein (bCRP) on CL/F, which was included in the previous model, was

considered irrelevant to UC and was removed based on lack of statistical significance in covariate re-evaluation. Also, formulation effect was fixed due to the use of only 1 formulation in Study GS-US-418-3898, which is the same as that in the RA Phase 3 studies and is the commercial formulation. No additional covariates were evaluated for this population. The final model parameters and the shrinkage estimates of the inter-individual variability (IIV) are presented in the tables below.

Table 7 Summary of Final Model Pharmacokinetic Parameters for Filgotinib.

	Final Parameter Estimate		Interindividual Variability/Residual Variability	
Parameter	**Typical Value**	**%RSE**	**Magnitude**	**%RSE**
$\exp(\theta_1)$: Apparent oral clearance for female (L/h), CL/F	41.0	1.30	27.0%	43.0
θ_{14}: Influence of male on CL/F	0.0371	17.3	--	--
θ_{15}: Influence of weight on CL/F and Q/F	0.75 [Fixed]	--	--	--
$\exp(\theta_2)$: Apparent central volume for white or Asian (L), V_c/F	101	0.20	40.0%	94.0
θ_{17}: Influence of other race on V_c/F	-0.146	28.9	--	--
θ_{18}: Influence of black race on V_c/F	-0.358	33.2	--	--
θ_{19}: Influence of weight on V_c/F and V_p/F	1 [Fixed]	--		
$\exp(\theta_5)$: Intercompartmental clearance (L/h)	2.44	1.80	--	--
$\exp(\theta_6)$: Apparent peripheral volume (L)	35.9	6.80	--	--
$\frac{\exp(\theta_1)}{\exp(\theta_2)} + \exp(\theta_3)$: Absorption rate constant for slower process (1/h)	2.13 [Fixed]	--	184%	3.30
$\exp(\theta_4)$: Duration (h), D1	0.629 [Fixed]	--	215%	1.60
$100 \times (1+\theta_{11})$: Capsule relative bioavailability (%)	66.0 [Fixed]	--	--	--
(θ_{10}): Mixture slower absorption	0.818 [Fixed]	--	--	--
$\omega^2_{CL/F,Vc/F}$: Covariance between CL/F and V_c/F	--	--	0.0327	176
Residual proportional variability (%)	43.3	1.10	--	--

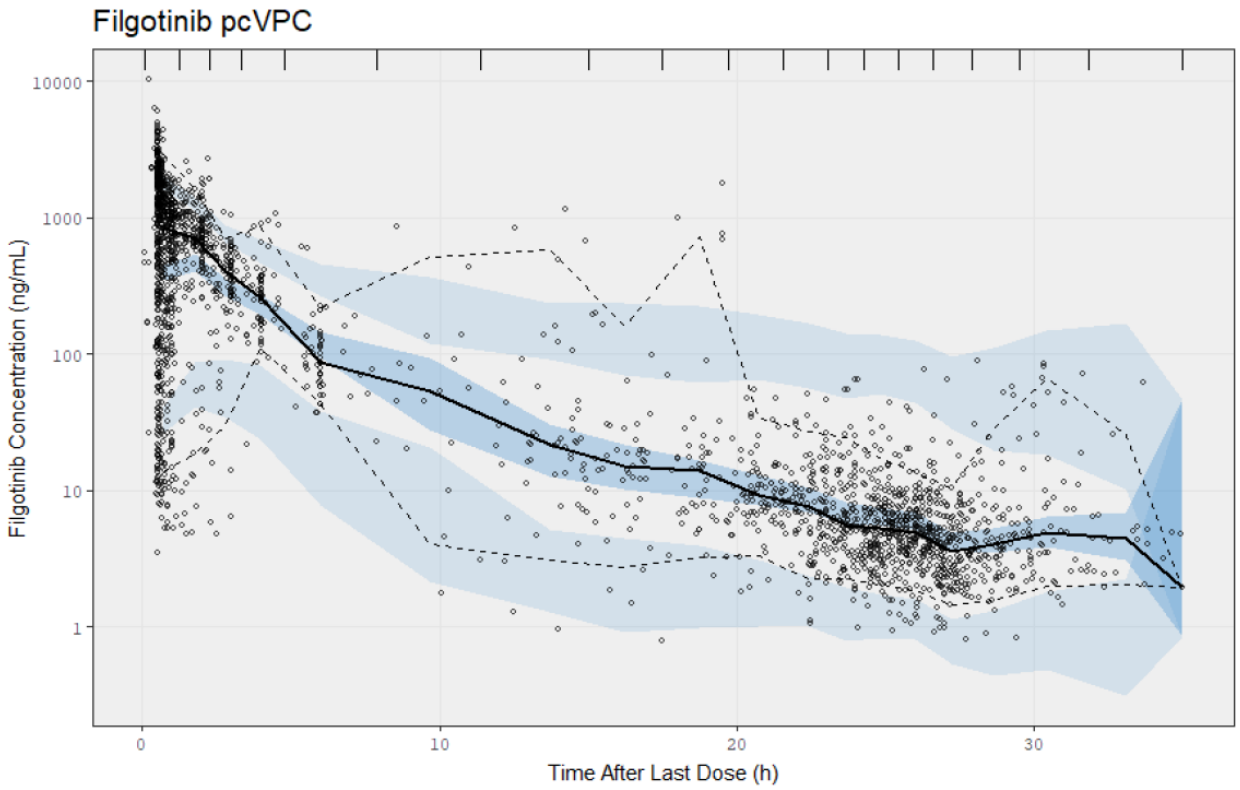
RSE = relative standard error; %RSE = relative standard error expressed as a percentage
Minimum Value of the Objective Function=X

Table 8 Shrinkage Estimates of IIV in the Final Filgotinib Model

Parameter	Parameter Description	Shrinkage (%)
$\omega_{CL/F}$	IIV of CL/F	23
$\omega_{Vc/F}$	IIV of V_c/F	57
ω_{ka}	IIV of k_a	51
ω_{D1}	IIV of D1	55
σ	Residual error (%)	20

σ = standard deviation of within-subject variability; ω = standard deviation of between-subject variability; IIV = interindividual variability

Model performance was assessed by prediction-corrected visual predictive check as displayed in Figure 2.



pcVPC = prediction-corrected visual predictive check
pcVPC plots show the median (solid line) and spread (5th to 95th percentile, dashed lines) of the observed concentrations in all subjects. The darker blue area is the 95% CI of the simulated median, and the lighter blue area is the 95% CI of the simulated 5th and 95th percentiles. Open circles show the observed data.

Figure 2 Filgotinib pcVPC Using the Final Model

Parameter estimates in this UC model were similar to those in the previous model for subjects with RA and healthy subjects. The post hoc individual exposures of filgotinib in subjects with UC were comparable with those in the subjects with RA, with a percent geometric mean ratio (%GMR) of 109.1%, 97.4%, and 142.2% for AUC_{tau}, C_{max}, and C_{tau}, respectively.

GS-829845 Model

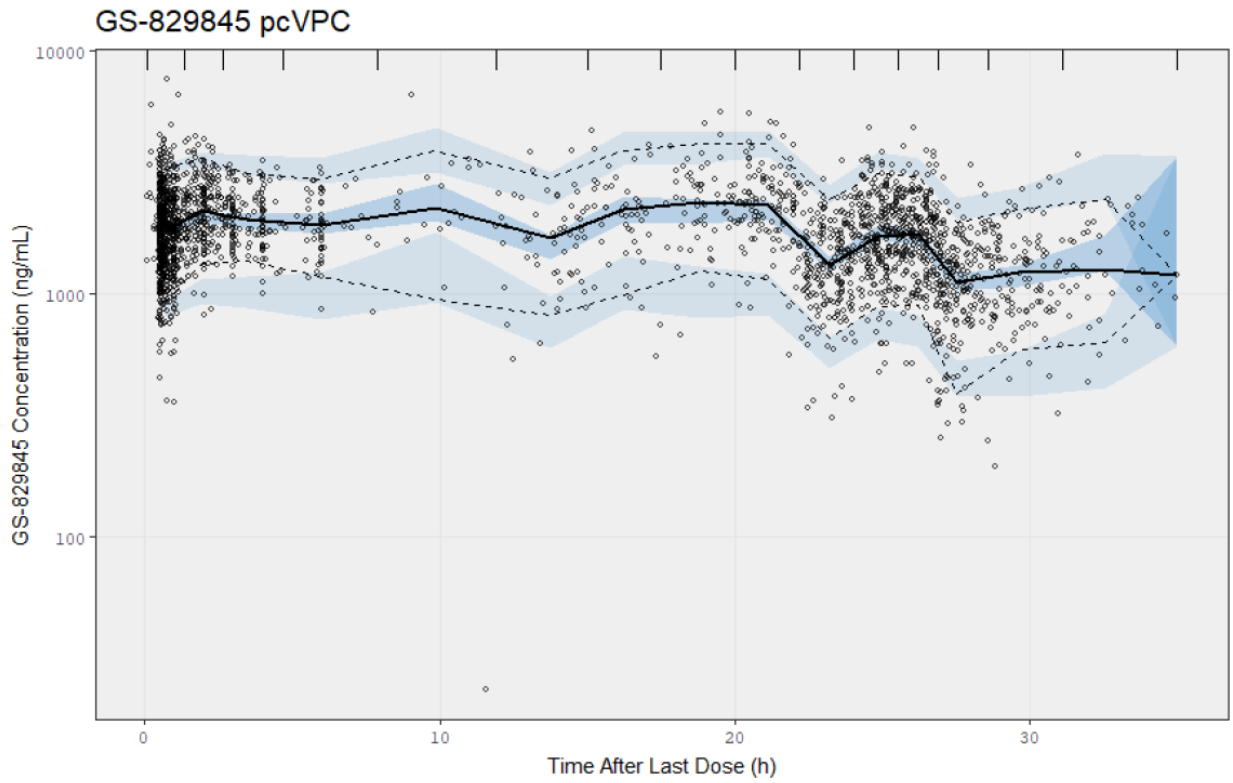
A summary of the GS-829845 PopPK Analysis datasets is presented in the table below.

Table 9 Summary of GS-829845 Concentration in the Population Pharmacokinetic Analysis Datasets in Study GS-US-418-3898

Analyte	Original Dataset		Model Evaluation Dataset		Model Development Dataset	
	Number of Subjects	Data Points	Number of Subjects	Data Points	Number of Subjects	Data Points
GS-829845	1023	2764	1023	2734	1010	2461

Source: Ad Hoc PopPK Table 10601.1

An external model validation using the previously developed model for RA and healthy subjects was used to predict the GS-829845 PK in subjects with UC. The previous model was a 1-compartment model with first-order absorption and first-order elimination. An IIV was included on CL/F, V_c/F, and k_a. Baseline creatinine clearance (bCL_{cr}), bCRP, subject status, and SEXF were identified as statistically significant covariates on CL/F, whereas RA duration, WT, and Asian race were identified as statistically significant covariates on V_c/F. In addition, formulation was found as a significant covariate on F. In subjects with UC, coefficient for RA duration was fixed to 0 and the formulation effect was fixed due to the use of only 1 formulation in Study GS-US-418-3898. No additional covariates were evaluated for this population for the GS-829845 model. The previously developed model adequately captured the observed GS-829845 plasma concentrations in subjects with UC, and parameter re-estimation was not necessary.



pcVPC = prediction-corrected visual predictive check
pcVPC plots show the median (solid line) and spread (5th to 95th percentile, dashed lines) of the observed concentrations in all subjects. The darker blue area is the 95% CI of the simulated median, and the lighter blue area is the 95% CI of the simulated 5th and 95th percentiles. Open circles show the observed data.

Figure 3 GS-829845 pcVPC Using External Validation

The post hoc individual GS-829845 exposures were similar between the subjects with UC and the subjects with RA, with a %GMR of 105.6%, 103.6%, and 108.7% for AUC_{tau}, C_{max}, and C_{tau}, respectively. A summary of the filgotinib and GS-829845 plasma exposures estimated based on the final model is provided in the table below.

Table 10 Summary of Mean/(%CV) of Filgotinib and GS-829845 Plasma Predicted Exposures in Subjects with UC and Comparison of Exposures between Different Populations

Analyte	PK Parameter	Mean Exposures in UC (%CV)	Mean Exposures in RA (%CV)	%GMR (90% CI) Subjects with UC vs Subjects with RA
Filgotinib	No of Subjects	N = 1001	N = 1987	--
	AUC_{tau} (h•ng/mL)	4932 (34.0)	5377 (28.9)	91.7 (90.1, 93.3)
	C_{max} (h•ng/mL)	1360 (43.2)	1327 (43.4)	102.7 (99.7, 105.8)
	C_{tau} (h•ng/mL)	9.20 (266)	12.0 (74.7)	70.3 (67.9, 72.9)
GS-829845	No of Subjects	N = 1010	N = 2009	--
	AUC_{tau} (h•ng/mL)	75786 (21.2)	80418 (23.2)	94.7 (93.4, 96.1)
	C_{max} (h•ng/mL)	3929 (18.1)	4083 (19.5)	96.5 (95.4, 97.7)
	C_{tau} (h•ng/mL)	2233 (29.0)	2454 (31.0)	92.0 (90.1, 93.8)

%CV = percentage coefficient of variation; GMR = geometric mean ratio; CI = confidence interval; PK = pharmacokinetic; UC = ulcerative colitis; RA = rheumatoid arthritis
Demographic PK Analysis Set included subjects with UC in Study GS-US-418-3898 and subjects with RA in Phase 3 Studies GS-US-417-0301, GS-US-417-0302, GS-US-417-0303, who were administered with the tablet formulation in the studies and were simulated with filgotinib 200 mg and had evaluable PK parameters from PopPK.

2.3.3. Pharmacodynamics

Mechanism of action

According to the MAH, cytokine signalling is a major component of innate and adaptive immune responses and aberrant cytokine receptor activation is associated with many chronic inflammatory conditions, including UC (Salas 2020). Inhibition of cytokine signalling via the disruption of the JAK-STAT pathway can target multiple processes involved in intestinal inflammation, cellular activation, proliferation of immune cells associated with UC, and disruption of immune homeostasis (cf Figure below). Filgotinib is being developed to inhibit intracellular signalling pathways associated with cytokine receptor activation.

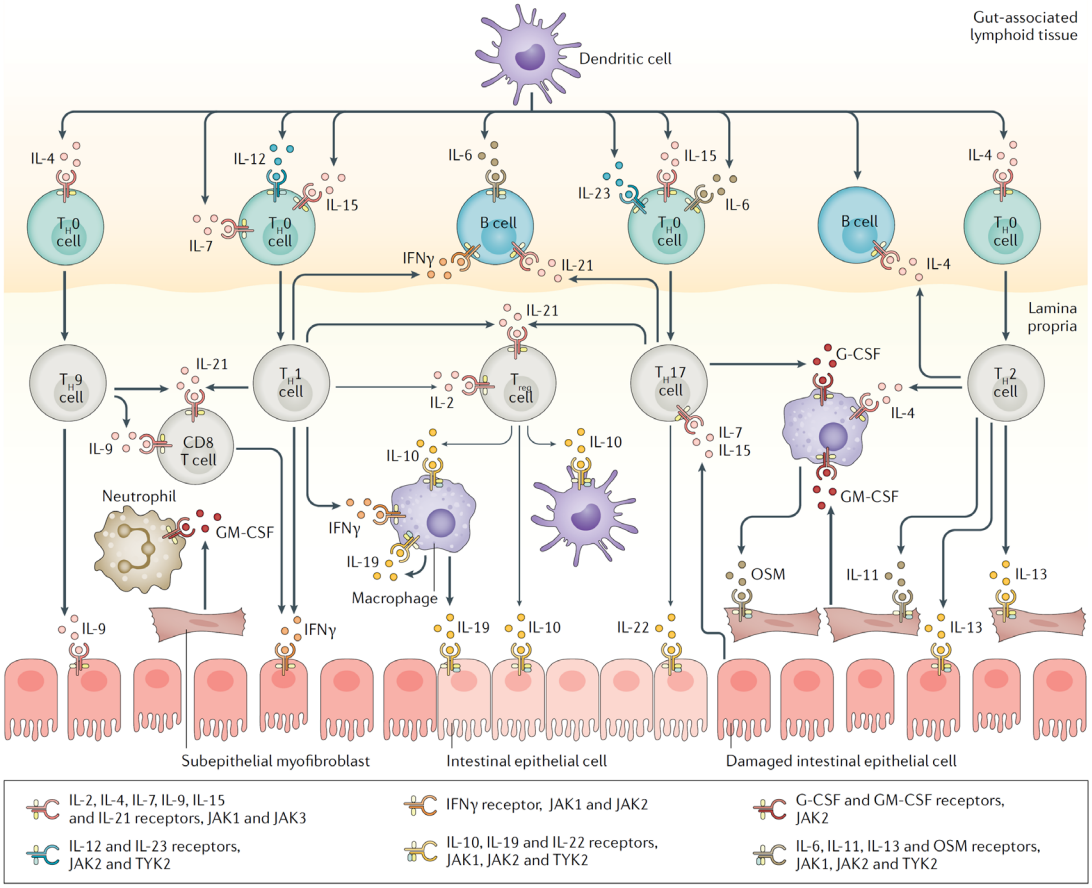


Figure 4 Pleiotropic Role of JAK-Associated Receptors in Inflammatory Bowel Disease

In vivo pharmacology has demonstrated that inhibition of JAK1 results in marked inhibition of pathways that drive intestinal STAT1 and STAT3 phosphorylation and in the reduction of disease activity in animal models of UC. In the mouse acute dextran sodium sulfate (DSS) model of UC, pharmacological inhibition of JAK1 with filgotinib demonstrated significant dose-dependent efficacy in improving body weight, fecal consistency, intestinal bleeding, and histological measures of colonic inflammation, as well as reducing serum inflammatory protein markers tissue inhibitor of metalloproteinase-1 (TIMP-1) and C-reactive protein (CRP). In the mouse chronic DSS model of UC, filgotinib was effective in improving body weight, fecal consistency and occult positivity (bleeding), in reducing colonic pSTAT3 levels and neutrophil and macrophage infiltrates, and in reducing serum inflammatory protein markers and chemoattractant factors. In the T cell adoptive transfer model of UC, co-administration of filgotinib with GS-829845 was used to model the pharmacodynamic pSTAT1/3 inhibition observed in human clinical studies. Co-administration of filgotinib and GS-829845 once daily resulted in improvements in body weight, fecal consistency, bleeding, colonic histology inflammation measures, and a reduction in colonic pSTAT1+ and pSTAT3+ cells. Additional homeostatic alterations in immune cellular subsets in blood, colon and spleen, and improvements in colonic inflammatory gene expression and cytokine levels were observed. According to the MAH, these *in vivo* studies demonstrate that filgotinib can markedly reduce intestinal inflammation in mouse models of UC.

Primary and secondary pharmacology

In both innate and adaptive immune cell-driven UC models of intestinal inflammation, filgotinib dosed alone or in combination with GS-829845, resulted in improvements of body weight, fecal consistency and bleeding with a reduction in colonic histological measures of inflammation, a reduction in colonic

pSTAT1 and pSTAT3 levels, a reduction in colonic inflammatory gene expression and tissue cytokines, immune cell subset homeostatic restoration, and a reduction in serum inflammatory proteins.

In both acute and chronic DSS models JAK target inhibition in the 30 mg/kg group was calculated to be at or below EC_{50} throughout the dosing period. In the adaptive T cell transfer model where filgotinib was co-dosed with GS-829845, target inhibition was above EC_{50} for approximately one quarter of the dosing interval. Target inhibition in the T cell transfer model most closely mirrors the predicted human pharmacodynamic pSTAT1/3 inhibition in UC patients. Consistent with a longer duration of inhibition, the improvements in disease activity and pharmacodynamic effects were more pronounced in the T cell transfer model. For example, both pSTAT1 and pSTAT3 were reduced in colons, nearly all histological measures of inflammation were significantly reduced, and extensive inhibition of inflammatory gene expression and tissue cytokines were observed.

2.3.4. PK/PD modelling

Exposure-response (ER) analyses were performed following completion of the Phase 2 study in subjects with Crohn's disease (CD) (GLPG0634-CL-211) to support dose selection for the Phase 2b/3 study, as well as on completion of the Phase 2b/3 study (GS US 418-3898), to confirm the dose proposed for commercialization. As both filgotinib and its metabolite, GS-829845, contribute to efficacy via JAK1 inhibition, their exposures were combined by accounting for relative inhibition potency in the analyses for efficacy, see equation below.

$AUC_{eff} = AUC_{tau\text{-}FIL} + AUC_{tau\text{-}met} * 1/10 * (425.51/357.43)$

Where $AUC_{tau\text{-}FIL}$ and $AUC_{tau\text{-}met}$ are the steady-state AUC_{tau} of filgotinib and GS-829845, respectively. The corresponding equation was used to calculate effective concentration (C_{eff}). Predicted exposures in terms of AUC_{eff} and C_{eff} were based on PopPK modelling.

The ER analyses for safety were performed separately for filgotinib and GS-829845 to characterize the individual safety profile of each analyte based on Phase 2b/3 data in subjects with UC.

Exposure-Response for Efficacy

Exposure-efficacy analyses were conducted for the primary efficacy endpoint of EBS remission at week 10 for the induction studies and at week 58 for the Maintenance Study. Additional secondary efficacy endpoints were also included in the exposure-efficacy analyses. The efficacy endpoints evaluated are summarized as follows:

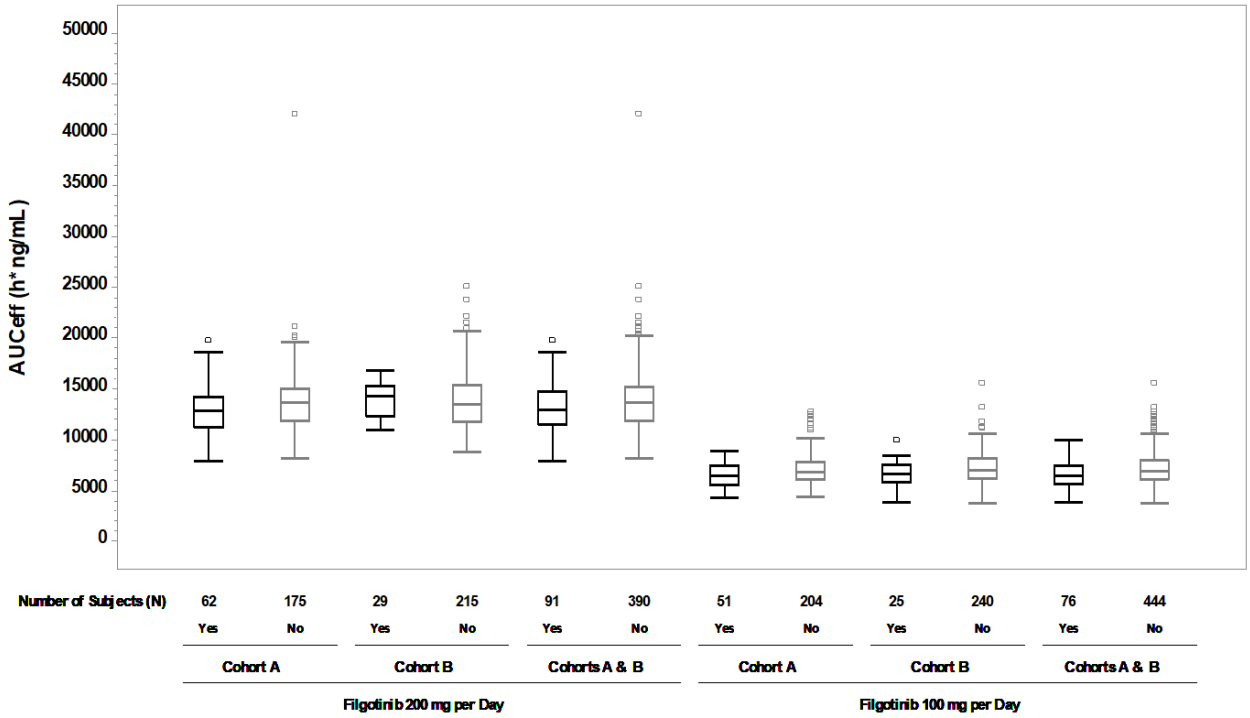
- Induction studies: EBS remission at Week 10 (primary), MCS remission, an endoscopic subscore of 0, Geboes histologic remission, and MCS remission (alternative definition)
- Maintenance Study: EBS remission at Week 58 (primary), MCS remission, an endoscopic subscore of 0, Geboes histologic remission, MCS remission (alternative definition), sustained EBS remission, and 6-month corticosteroid-free EBS remission

The PK/PD Analysis Set for PK-efficacy included subjects with UC who received filgotinib and had evaluable PopPK-based exposure estimates (AUC_{eff} and C_{eff}) for both filgotinib and GS-829845 (N = 1001 for the induction studies and N = 362 for the Maintenance Study).

Induction Studies

In the induction studies, exposure-efficacy relationships were evaluated by comparing AUC_{eff} in subjects who achieved and who did not achieve EBS remission at Week 10 by dose (Figure 5). The AUC_{eff} overlapped between subjects who achieved (black) and subjects who did not achieve (gray) EBS

remission within each dose, for Cohort A (biologic-naive subjects), Cohort B (biologic-experienced subjects), or combined Cohorts A and B, indicating a lack of ER relationship within each dose.



EBS = endoscopy/bleeding/stool frequency; PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; UC = ulcerative colitis
PK/PD analysis set includes subjects with UC who were enrolled/randomized, received at least 1 dose of filgotinib in the induction studies of GS-US-418-3898, and had at least 1 nonmissing PK parameter of interest.
For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 × the interquartile range) are displayed as small squares.
AUC_{eff} = AUC_{tau} of filgotinib + AUC_{tau} of GS-829845 *1/10 * (425.51/357.43).

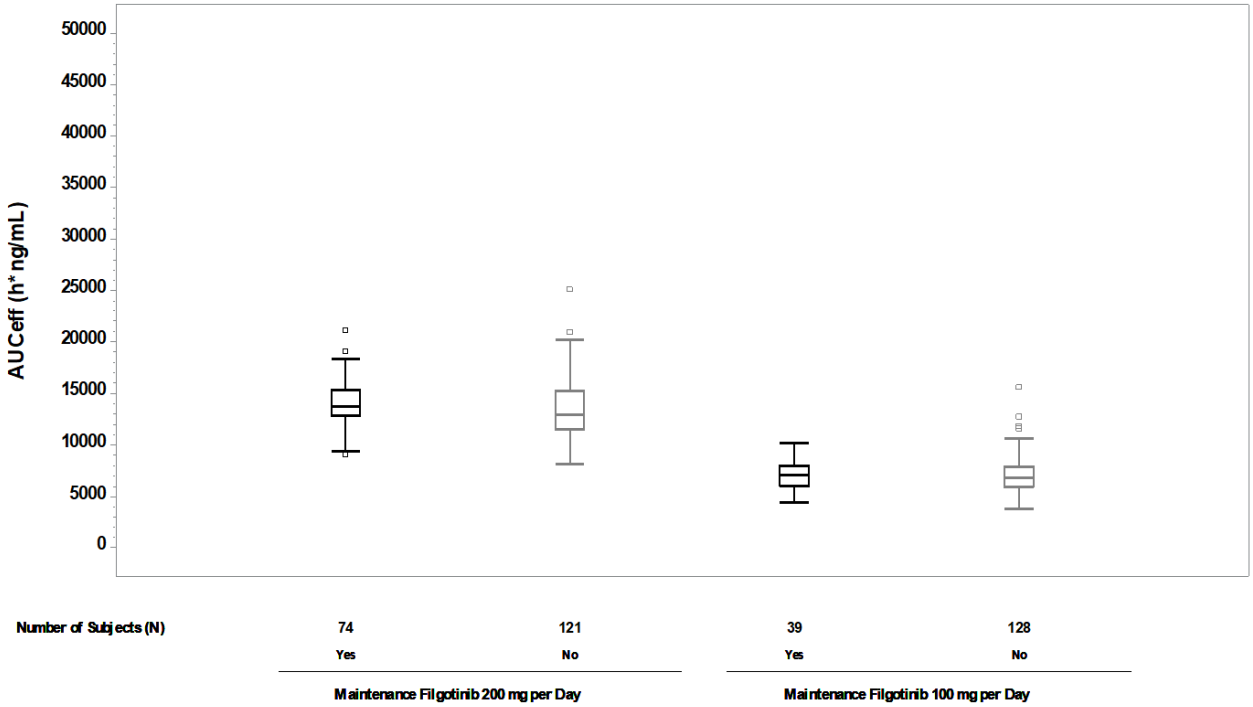
Figure 5 Induction Studies: AUCeff in Subjects with UC by EBS Remission Status and Filgotinib Dose at Week 10 (PK/PD Analysis Set, Study GS-US-418-3898)

Additional graphical analyses based on MCS remission, an endoscopic subscore of 0, Geboes histologic remission, and MCS remission (alternative definition) against AUC_{eff} and EBS remission against $C_{eff,}$ did not show an exposure-efficacy relationship within each dose.

Maintenance Study

In the Maintenance Study, AUC_{eff} also overlapped between those who achieved (black) and those who did not achieve (gray) EBS remission within each dose, indicating a lack of ER relationship within each dose (Figure 6).

Exposure-efficacy graphical analyses combining data from the 2 doses of filgotinib showed a positive relationship between the proportions of subjects who achieved EBS remission and the AUC_{eff} quartile groups in the Maintenance Study (Figure 7).



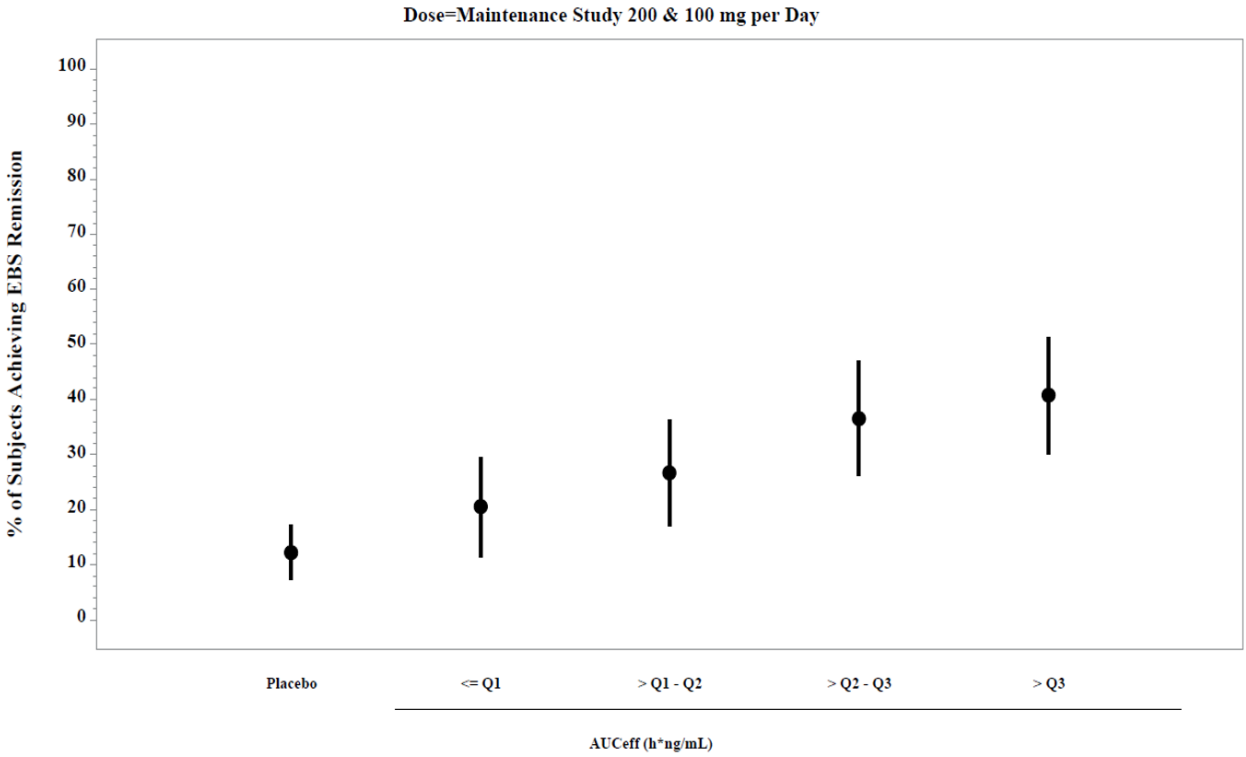
EBS = endoscopy/bleeding/stool frequency; PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; UC = ulcerative colitis

PK/PD analysis set includes subjects with UC who were enrolled/randomized, received at least 1 dose of filgotinib in the Maintenance Study of GS-US-418-3898, and had at least 1 nonmissing PK parameter of interest.

For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 × the interquartile range) are displayed as small squares.

AUC_{eff} = AUC_{tau} of filgotinib + AUC_{tau} of GS-829845 *1/10 * (425.51/357.43).

Figure 6 Maintenance Study: AUC_{eff} in Subjects with UC by EBS Remission Status and Filgotinib Dose at Week 58 (PK/PD Analysis Set, Study GS-US-418-3898)



CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; UC = ulcerative colitis
PK/PD analysis set includes subjects with UC who were enrolled/randomized, received at least 1 dose of filgotinib in the Maintenance Study of GS-US-418-3898, and had at least 1 nonmissing PK parameter of interest.
The vertical line represents the 95% CI for the proportion within each group based on the normal approximation method with a continuity correction.
AUC_{eff} = AUC_{tau} of filgotinib + AUC_{tau} of GS-829845 *1/10 * (425.51/357.43).

Figure 7 Maintenance Study: Proportion of Subjects with UC Who Achieved EBS Remission by AUCeff Quartile Group (PK/PD Analysis Set and Placebo Subjects, Study GS US 418 3898)

Additional graphical analyses based on MCS remission, an endoscopic subscore of 0, Geboes histologic remission, MCS remission (alternative definition), 6-month corticosteroid-free EBS remission, and sustained EBS remission against AUC_{eff} and EBS remission against C_{eff} did not show an exposure-efficacy relationship within each dose.

Exposure-Response for Safety

The ER analyses for safety were based on the pooled population across biologic-naive and biologic-experienced subjects and were performed separately for filgotinib and GS-829845 to characterize the individual safety profiles of each analyte. The filgotinib exposures (AUC_{tau}) were compared in pooled subjects across the filgotinib 200 mg and 100 mg groups between who experienced and who did not experience the selected safety events.

The 5 most frequent treatment-emergent adverse events (TEAEs) that occurred in the filgotinib 200 mg once daily group in the induction studies combined and in the Maintenance Study (GS-US-418-3898 Final) were selected for evaluation in the ER analyses for safety. Similarly, the 5 most frequent Grade 3 or 4 laboratory abnormalities that occurred in the filgotinib 200 mg once daily group in the induction studies combined and in the Maintenance Study (GS-US-418-3898 Final) were also evaluated. In the event that 2 or more safety endpoints of interest shared the same occurrence, they were all included in the analyses. Accordingly, 6 TEAEs in total were evaluated for both the induction

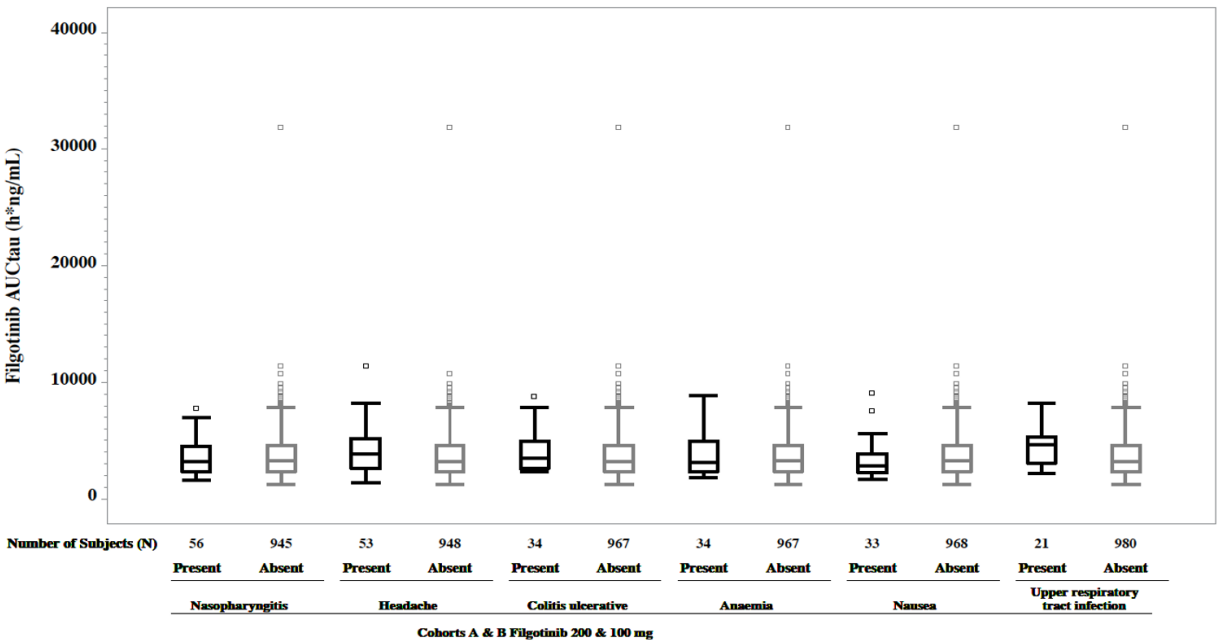
studies combined and for the Maintenance Study, while 6 and 5 Grade 3 or 4 laboratory abnormalities were evaluated for the induction studies combined and the Maintenance Study, respectively.

Safety endpoints evaluated are summarized as follows:

- TEAEs in the induction studies: headache (5.9%), nasopharyngitis (5.3%), colitis ulcerative (5.3%), anemia (3.7%), nausea (3.0%), and upper respiratory tract infection (3.0%).
- Grade 3 or 4 laboratory abnormalities in the induction studies: phosphate decrease (3.6%), lymphocyte decrease (2.2%), hemoglobin decrease (2.0%), creatine kinase increase (1.4%), neutrophil decrease (0.6%), and white blood cell (WBC) decrease (0.6%).
- TEAEs in the Maintenance Study: nasopharyngitis (10.9%), colitis ulcerative (10.4%), upper respiratory tract infection (5.4%), arthralgia (4.0%), abdominal pain (4.0%), and back pain (4.0%).
- Grade 3 or 4 laboratory abnormalities in the Maintenance Study: creatine kinase increase (4.0%), phosphate decrease (2.5%), lymphocyte decrease (2.5%), hemoglobin decrease (1.5%), and serum potassium increase (1.5%).

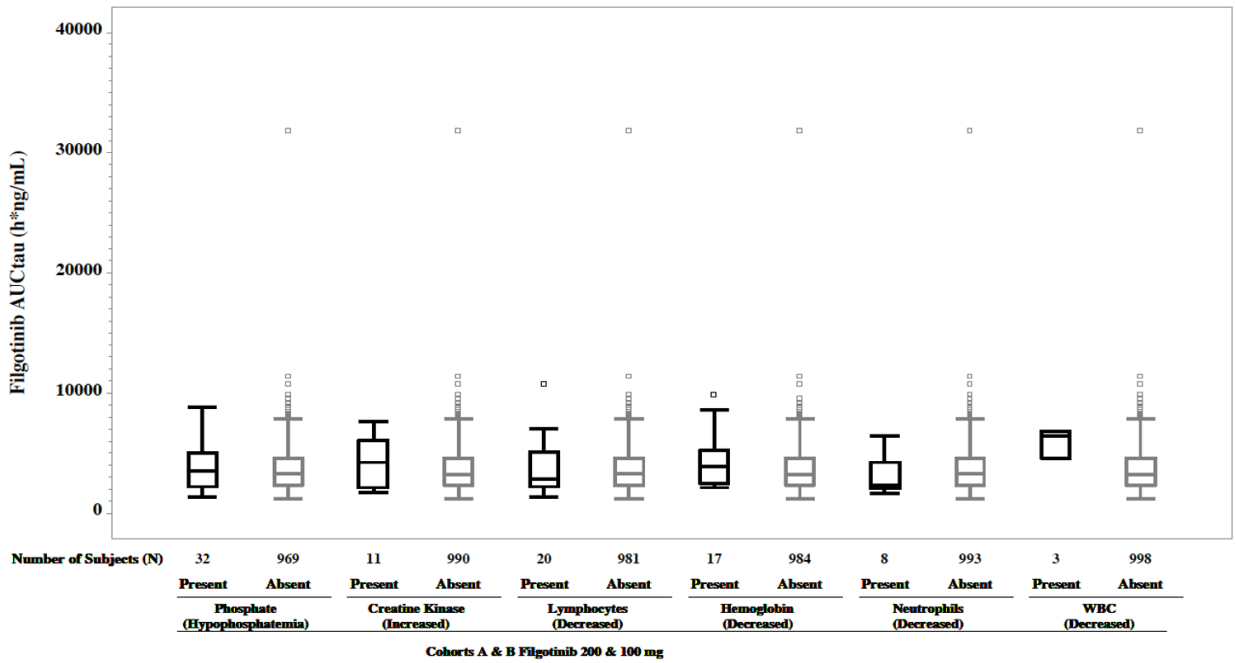
Filgotinib Induction Studies: Most Frequent Adverse Events and the Most Frequent Grade 3 or 4 Laboratory Abnormalities

As shown in Figure 8, there was no consistent trend between filgotinib exposures (AUC_{tau}) and the presence (black) or absence (gray) of the most frequent TEAEs in the induction studies. Similarly, highly overlapping AUC_{tau} was observed between subjects who experienced (black) and who did not experience (gray) the most frequent Grade 3 or 4 laboratory abnormalities (Figure 9).



PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; TEAE = treatment-emergent adverse event; UC = ulcerative colitis
PK/PD analysis set includes subjects with UC who were enrolled/randomized, received at least 1 dose of filgotinib in the induction studies of GS-US-418-3898, and had at least 1 nonmissing PK parameter of interest.
For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 × the interquartile range) are displayed as small squares.
AUC_{tau} is the population PK-predicted exposure in Phase 2b/3 subjects with UC receiving filgotinib.

Figure 8 Induction Studies: Filgotinib AUC_{tau} by the Most Frequent TEAEs in Subjects with UC (PK/PD Analysis Set, Study GS-US-418-3898)

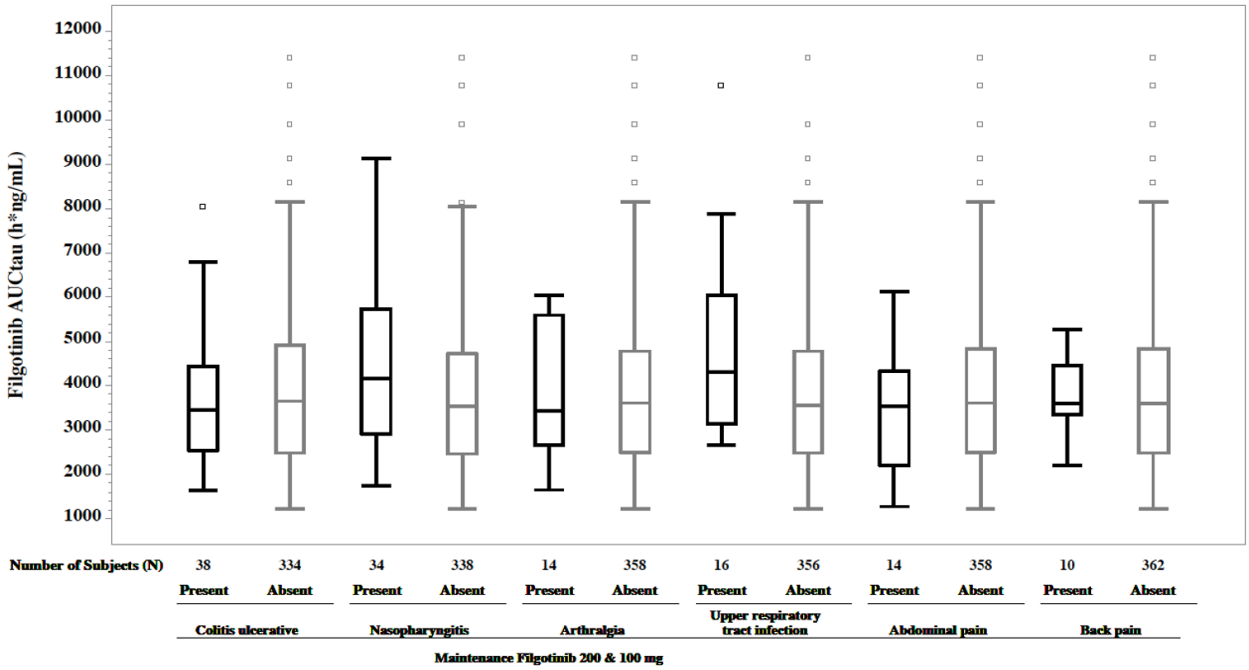


PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; UC = ulcerative colitis; WBC = white blood cell
PK/PD analysis set includes subjects with UC who were enrolled/randomized, received at least 1 dose of filgotinib in the induction studies of GS-US-418-3898, and had at least 1 nonmissing PK parameter of interest.
For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 × the interquartile range) are displayed as small squares.
AUC_{tau} is the population PK-predicted exposure in Phase 2b/3 subjects with UC receiving filgotinib.

Figure 9 Induction Studies: Filgotinib AUC_{tau} by the Most Frequent Grade 3 or 4 Laboratory Abnormalities in Subjects with UC (PK/PD Analysis Set, Study GS-US-418-3898)

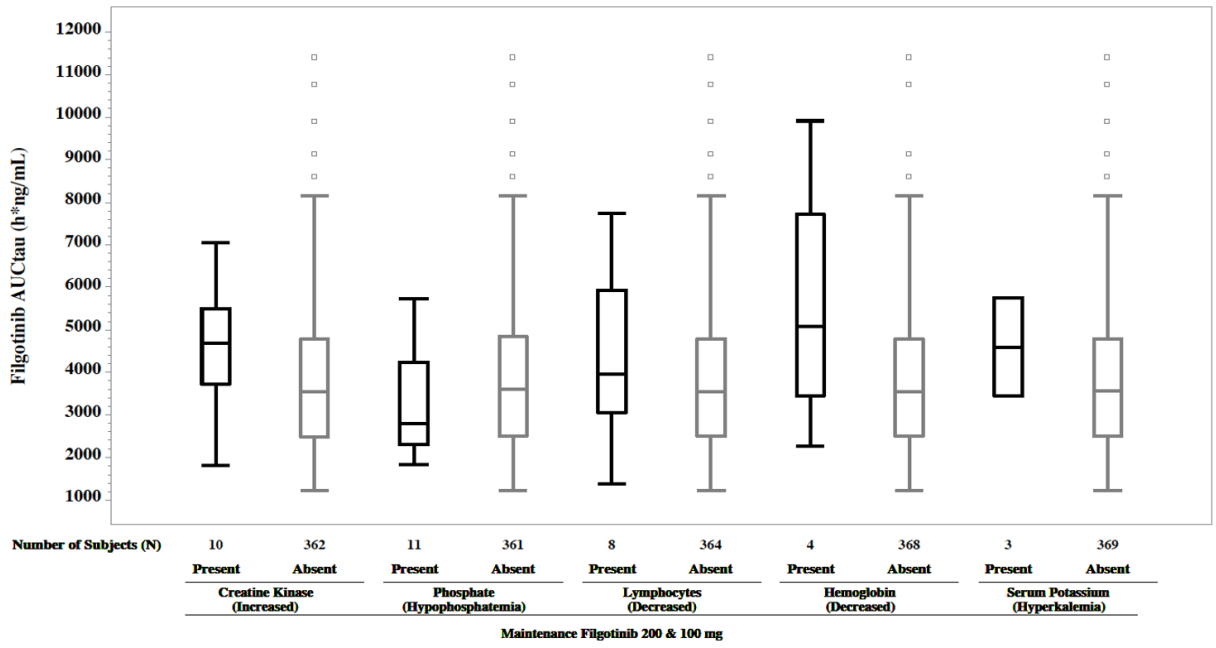
Filgotinib Maintenance Study: Most Frequent Adverse Events and the Most Frequent Grade 3 or 4 Laboratory Abnormalities

As shown in Figure 10, there was no consistent trend between filgotinib exposures (AUC_{tau}) and the presence (black) or absence (gray) of the evaluated TEAEs in the Maintenance Study. Similarly, highly overlapping AUC_{tau} values were observed between subjects who experienced (black) and who did not experience (gray) the selected Grade 3 or 4 laboratory abnormalities, albeit there was a high data variability due to small sample size (N < 12) for subjects who experienced Grade 3 or 4 laboratory abnormalities (Figure 11).



PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; TEAE = treatment-emergent adverse event; UC = ulcerative colitis
PK/PD analysis set includes subjects with UC who were enrolled/randomized, received at least 1 dose of filgotinib in the Maintenance Study of GS-US-418-3898, and had at least 1 nonmissing PK parameter of interest.
For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 × the interquartile range) are displayed as small squares.
AUC_{tau} is the population PK-predicted exposure in Phase 2b/3 subjects with UC receiving filgotinib.

Figure 10 Maintenance Study: Filgotinib AUC_{tau} by the Most Frequent TEAEs in Subjects with UC (PK/PD Analysis Set, Study GS-US-418-3898)

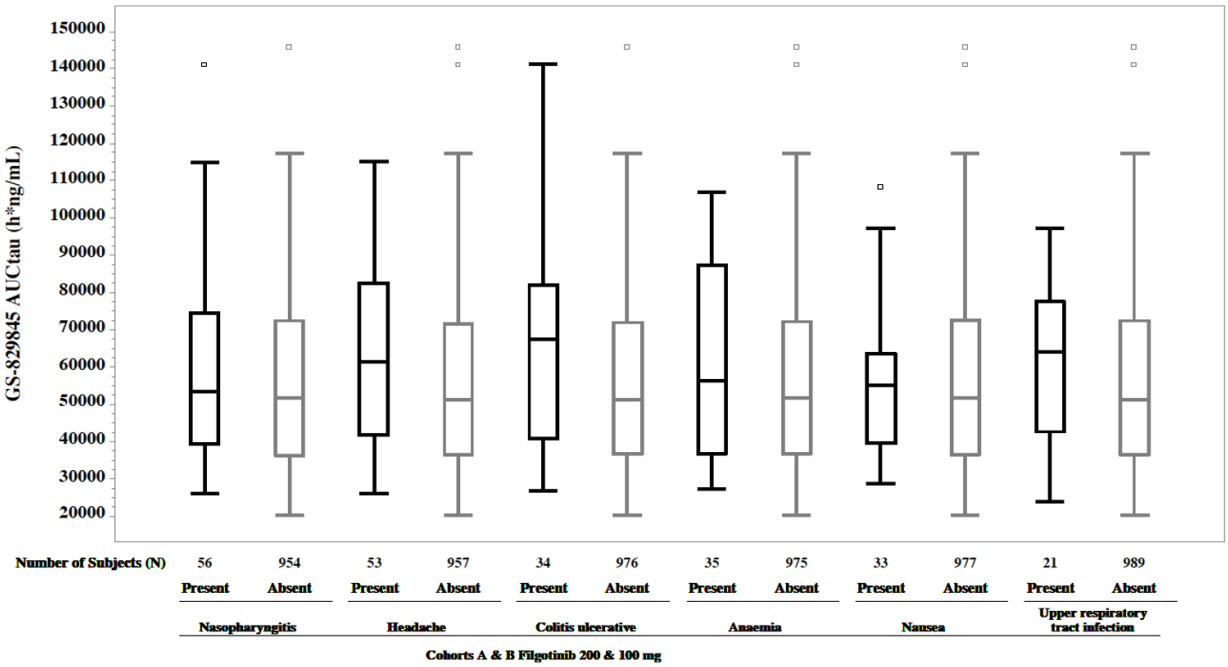


PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; UC = ulcerative colitis
PK/PD analysis set includes subjects with UC who were enrolled/randomized, received at least 1 dose of filgotinib in the Maintenance Study of GS-US-418-3898, and had at least 1 nonmissing PK parameter of interest.
For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 × the interquartile range) are displayed as small squares.
AUC_{tau} is the population PK-predicted exposure in Phase 2b/3 subjects with UC receiving filgotinib.

Figure 11 Maintenance Study: Filgotinib AUC_{tau} by the Most Frequent Grade 3 or 4 Laboratory Abnormalities in Subjects with UC (PK/PD Analysis Set, Study GS-US-418-3898)

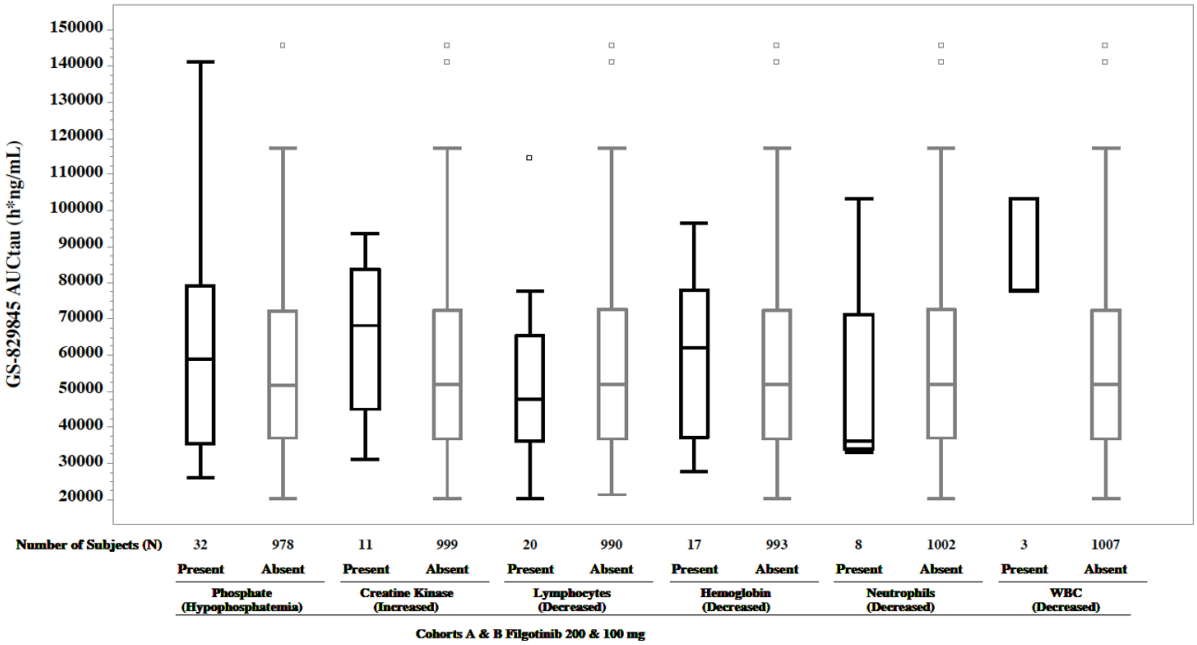
GS-829845 Induction Studies: Most Frequent Adverse Events and the Most Frequent Grade 3 or 4 Laboratory Abnormalities

GS-829845 exposures (AUC_{tau}) were highly overlapping between subjects who experienced (black) and who did not experience (gray) the most frequent TEAEs in the induction studies as shown in Figure 12. A similar finding was observed for the most frequent Grade 3 or 4 laboratory abnormalities (Figure 13). Of note, the sample size was small for certain Grade 3 or 4 laboratory abnormalities (eg, N = 8 for neutrophil decrease and N = 3 for WBC decrease) and thus, analyses in these groups may not be conclusive.



PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; TEAE = treatment-emergent adverse event; UC = ulcerative colitis
PK/PD analysis set includes subjects with UC who were enrolled/randomized, received at least 1 dose of filgotinib in the induction studies of GS-US-418-3898, and had at least 1 nonmissing PK parameter of interest.
For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 × the interquartile range) are displayed as small squares.
AUC_{tau} is the population PK-predicted exposure in Phase 2b/3 subjects with UC receiving filgotinib.

Figure 12 Induction Studies: GS-829845 AUC_{tau} by the Most Frequent TEAEs in Subjects with UC (PK/PD Analysis Set, Study GS-US-418-3898)

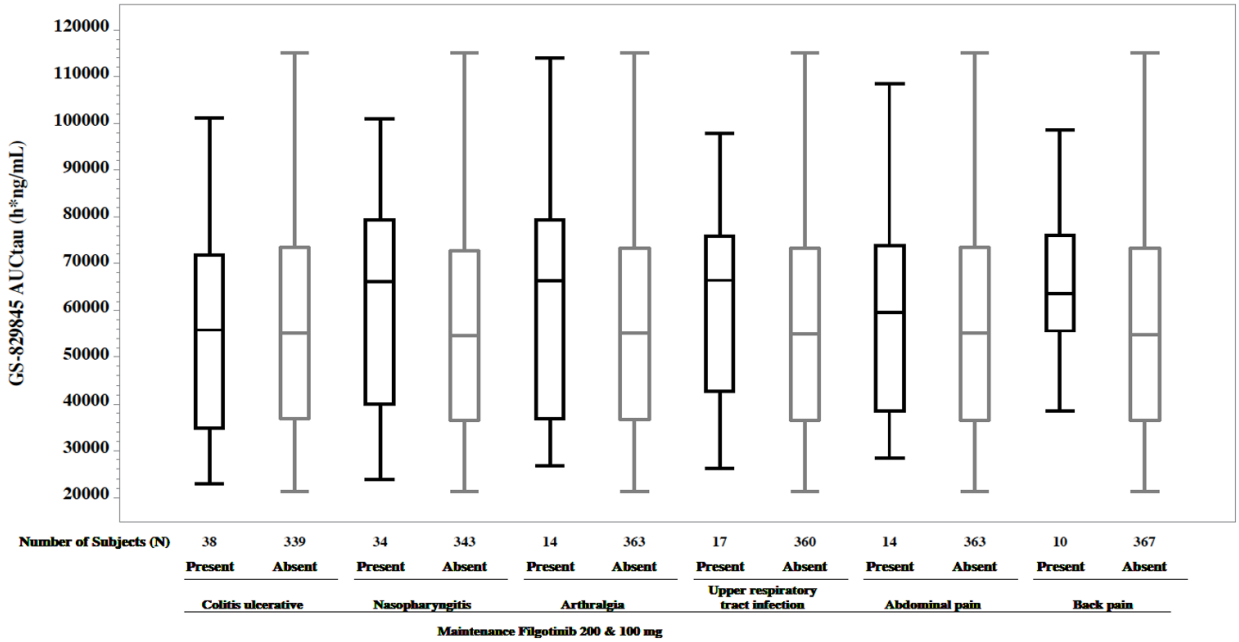


PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; UC = ulcerative colitis; WBC = white blood cell
PK/PD analysis set includes subjects with UC who were enrolled/randomized, received at least 1 dose of filgotinib in the induction studies of GS-US-418-3898, and had at least 1 nonmissing PK parameter of interest.
For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 × the interquartile range) are displayed as small squares.
AUC_{tau} is the population PK-predicted exposure in Phase 2b/3 subjects with UC receiving filgotinib.

Figure 13 Induction Studies: GS-829845 AUC_{tau} by the Most Frequent Grade 3 or 4 Laboratory Abnormalities in Subjects with UC (PK/PD Analysis Set, Study GS-US-418-3898)

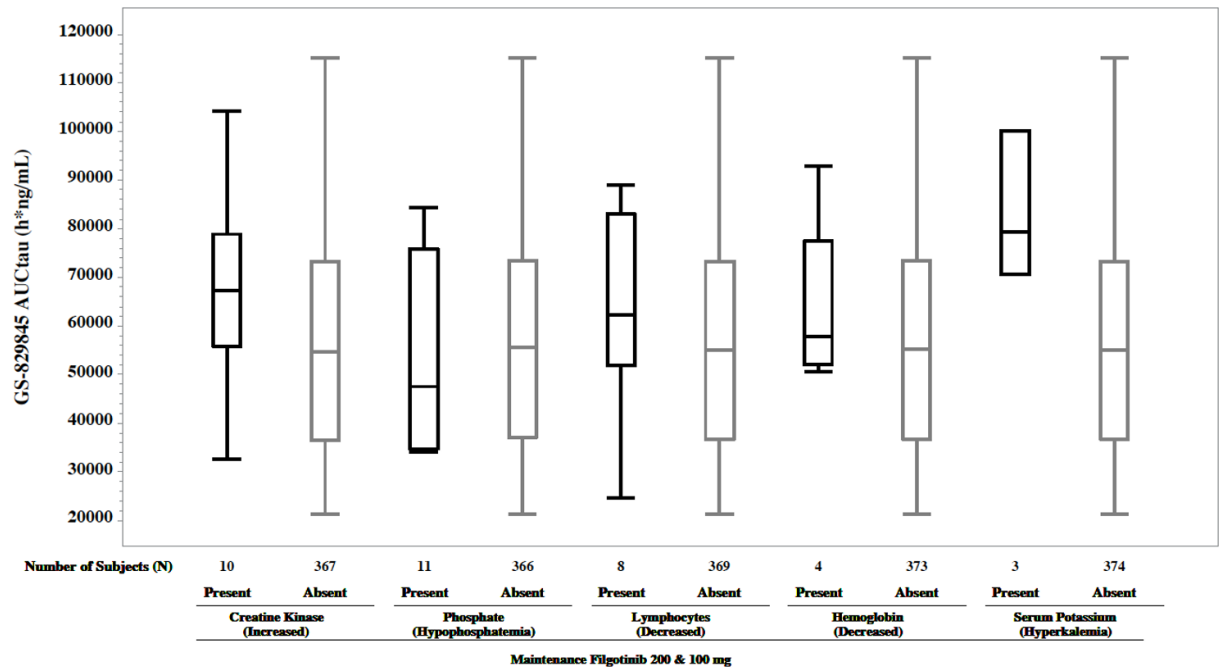
GS-829845 Maintenance Study: Most Frequent Adverse Events and the Most Frequent Grade 3 or 4 Laboratory Abnormalities

GS-829845 exposures (AUC_{tau}) were highly overlapping between subjects who experienced (black) and who did not experience (gray) the selected TEAEs in the Maintenance Study as shown in Figure 14. A similar finding was observed for Grade 3 or 4 laboratory abnormalities. It is worth mentioning that higher data variability was noted, particularly for Grade 3 or 4 laboratory abnormalities, due to small sample size (N < 12) of subjects who experienced selected Grade 3 or 4 laboratory abnormalities.



PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; TEAE = treatment-emergent adverse event; UC = ulcerative colitis
PK/PD analysis set includes subjects with UC who were enrolled/randomized, received at least 1 dose of filgotinib in the Maintenance Study of GS-US-418-3898, and had at least 1 nonmissing PK parameter of interest.
For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 × the interquartile range) are displayed as small squares.
AUC_{tau} is the population PK-predicted exposure in Phase 2b/3 subjects with UC receiving filgotinib.

Figure 14 Maintenance Study: GS-829845 AUC_{tau} by the Most Frequent TEAEs in Subjects with UC (PK/PD Analysis Set, Study GS-US-418-3898)



PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; UC = ulcerative colitis
PK/PD analysis set includes subjects with UC who were enrolled/randomized, received at least 1 dose of filgotinib in the Maintenance Study of GS-US-418-3898, and had at least 1 nonmissing PK parameter of interest.
For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 × the interquartile range) are displayed as small squares.
AUC_{tau} is the population PK-predicted exposure in Phase 2b/3 subjects with UC receiving filgotinib.

Figure 15 Maintenance Study: GS-829845 AUC_{tau} by the Most Frequent Grade 3 or 4 Laboratory Abnormalities in Subjects with UC (PK/PD Analysis Set, Study GS-US-418-3898)

2.3.5. Discussion on clinical pharmacology

The main investigation of filgotinib's PK properties was assessed and reported in the initial marketing authorisation application (i.e. the RA indication). Population PK analyses of filgotinib and GS-829845 evaluated data from a Phase 2b/3 clinical study in subjects with UC (GS-US-418-3898). Intensive PK samples were collected in 41 subjects and sparse PK samples were collected in 1001/1010 (parent/metabolite) subjects. The filgotinib population PK model for the RA population was used as the basis for the UC population model. The external validation of the RA model indicated that the model did not adequately describe UC subject data. Subsequently, the model parameters were re-estimated and the bCRP covariate (RA specific) was removed from the model. However, systematic underprediction of C_{max} is still present in the final model. Furthermore, the uncertainty estimates (%RSE) are unreasonably low (<2%) for several model parameters and the condition number (highest divided by lowest eigenvalue) for the model is >300 000 indicating that the model has severe stability issues. In addition, the covariate 'other race' on volume of distribution have a confidence interval that includes zero (bootstrap results), suggesting that the covariate is not informative and should be removed from the model. The model stability issues as well as the inability to describe the absorption phase (and subsequently C_{max}) were also present in the RA model and subsequently, in the RA submission the population PK results were not considered reliable. The population PK analysis for the metabolite GS-289845 is considered adequate.

In summary, the filgotinib PK model for UC subjects is not considered reliable by the CHMP. However, as this issue was already identified during the initial MAA and there is sufficient clinical data to support the dose selection, the issues with the filgotinib PK model have not be further pursued by the CHMP. An NCA analysis for patients with ulcerative colitis was requested by CHMP in order to consistently compare the expected exposure between the patients with different diseases, doses and methods. Additionally, the MAH was asked to provide graphical presentation of the observed PK data stratified on dose. Furthermore, it was pointed out by CHMP that predefined criteria used for assessing clinical relevance are required. An NCA analysis of PK data from 13 UC patients was submitted in the response to CHMP questions and the results indicate that filgotinib exposure increased more than dose proportionally after administration of 200 mg filgotinib. Furthermore, the results indicate that the disproportional increase in exposure is slightly more pronounced in patients with ulcerative colitis compared to those with rheumatoid arthritis (2.7-times vs. 2.5-times, respectively). Nonetheless, it should be kept in mind that the overall number of patients with ulcerative colitis included in this analysis is very small (n=13, 200 mg dose), thus results should be interpreted with caution. Overall, the CHMP concluded that these results were acceptable from a PK perspective considering the data gathered in the clinical study using the proposed dosing regimen in patients with ulcerative colitis.

Graphical exposure-response analyses have been performed based on predicted exposure based on the population PK analyses. Due to the issues identified with the filgotinib population PK analysis, the reliability of the predicted exposure is uncertain and thus, the results from the exposure-response analyses should be interpreted with caution.

Exposure-efficacy relationships has been explored with a combined exposure for filgotinib and the active metabolite GS-289845 which is the same approach as was used in the initial MAA. For both induction and maintenance treatment, the graphical analyses of exposure-response indicate that there is no difference in exposure between responders and non-responders within each dose. For the full exposure range (exposures from both maintenance doses combined), a trend of increasing efficacy with increasing exposure was visible supporting that an increased dose leads to an increase in efficacy.

Graphical exploration of exposure-safety relationships has been performed separately for filgotinib and the active metabolite GS-289845 which is acceptable. However, it should be noted that there is a concern regarding the reliability of predicted filgotinib exposure and as such the exposure-response relationships should be interpreted with caution.

In summary, although the exposure-response analyses are not considered pivotal for dose selection in the UC population, the CHMP concluded that the results support that an increased dose results in increased efficacy and no unexpected or concerning exposure-safety trends were apparent.

2.3.6. Conclusions on clinical pharmacology

The filgotinib PK model for UC subjects is not considered reliable by the CHMP. However, as this issue was already identified during the initial MAA and there is sufficient clinical data to support the dose selection, the issues with the filgotinib PK model have not be further pursued by the CHMP.

Section 5.2 of the SmPC has been adequately updated with information on PK parameters in UC. Overall, the CHMP concluded that the new UC indication was acceptable from a PK perspective.

2.4. Clinical efficacy

2.4.1. Dose response study

No Phase 2 dose-ranging studies were conducted with filgotinib in subjects with moderately to severely active UC. The doses evaluated in the UC program were based on the results of a Phase 2 Study GLPG0634-CL-211 (FITZROY) evaluating the safety and efficacy of filgotinib in subjects with moderately to severely active Crohn's disease (CD). An overview and a summary of the results of the FITZROY study are included below:

Study GLPG0634-CL-211 (FITZROY): Double-blind, randomized, placebo-controlled, multi-centre study to investigate the efficacy and safety of GLPG0634 in subjects with active Crohn's disease with evidence of mucosal ulceration

Methods

The study design was a double-blind, randomized, placebo-controlled, multi-center Phase II study. It comprised 2 parts (Figure below). The treatment assignment was blinded for the full 20 weeks study duration.

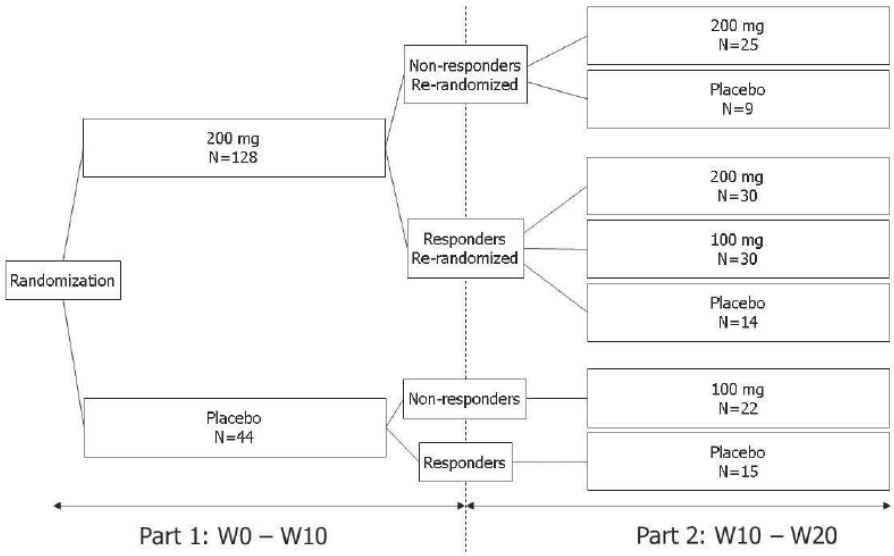


Figure 16 - Study GLPG0634-CL-211 (FITZROY) study diagram

At baseline, eligible subjects with documented history ileal, colonic or ileo-colonic CD, with of moderate to severe active disease (CDAI score during screening ≥ 220 to ≤ 450) and with evidence of active inflammation as demonstrated by endoscopic confirmation of active disease were randomized in a 3:1 ratio to receive either filgotinib 200 mg QD or placebo for 10 weeks. Based on their clinical response in Part 1, subjects in Part 2 either continued their current treatment or were reassigned to a different treatment (filgotinib 100 mg QD or placebo) for an additional 10 weeks. Clinical response was defined as a reduction in CDAI of ≤ -100 points.

The filgotinib study medication was presented as an oral brown film-coated tablet containing filgotinib as HCl-salt equivalent to 100 mg filgotinib. It was administered with a glass of water daily in the morning.

Subjects receiving mesalazine and olsalazine, or oral steroids for UC (≤30 mg prednisolone equivalent/day or budesonide dose ≤9 mg/day) were eligible provided they were on a stable dose for the required period of time. Previous exposure to immunomodulators (e.g., thiopurines and MTX) was permitted, but had to be discontinued at least 25 days prior to the first dose. Subjects previously not exposed to anti-TNF treatment (TNF-naïve) and subjects previously exposed to anti-TNF therapy (infliximab, adalimumab, or certolizumab pegol) at a dose registered for the treatment of CD were both eligible, but anti-TNFs had to be discontinued at least 8 weeks prior to Baseline. Subjects deemed by the treating physician as a primary or secondary non-responder or intolerant to anti-TNF treatment or responders to anti-TNF treatment where treatment was stopped for other reasons (TNF-experienced) could also be included.

The stratification factors in the randomization process were:

Part 1:

- anti-TNF naïve or anti-TNF experienced (responder and non-responder) (50%/50% fixed strata)

- Screening CRP ≤ 10mg/L / Screening CRP > 10 mg/L

- oral glucocorticosteroids use at Baseline (yes/no).

- Part 2:

- clinical response (yes/no) at Week 10

- anti-TNF naïve or anti-TNF experienced (responder and non-responder)

- oral glucocorticosteroids use at Baseline (yes/no).

The primary objective was to demonstrate efficacy in terms of the percentage of subjects achieving clinical remission (defined as a CDAI score < 150) following 10 weeks treatment with filgotinib 200 mg q.d. versus placebo in subjects with active CD with evidence of mucosal ulceration.

The secondary objectives were:

1. To evaluate the efficacy in terms of percentage of subjects achieving clinical response, clinical remission, endoscopic response, endoscopic remission, and mucosal healing with filgotinib given q.d. compared to placebo.

    Clinical response was defined as a decrease in CDAI of at least 100 points versus Baseline.

    Endoscopic remission was defined as a SES-CD score ≤ 4, with ulcerated surface subscore no greater than 1 in any segment.

    Endoscopic response was defined as a reduction of SES-CD score by at least 50% versus Baseline.

    Mucosal healing was defined as a SES-CD score equal to 0.

2. To assess the effect of filgotinib (compared to placebo) on subject's quality of life using the Inflammatory Bowel Disease Questionnaire (IBDQ).

3. To evaluate the safety and tolerability of filgotinib given to subjects with CD.

4. To characterize the pharmacokinetics (PK) of filgotinib and its metabolite (G254445) in subjects with CD.

5. To assess the effects of filgotinib on selected pharmacodynamic (PD) biomarkers (eg, C-reactive protein [CRP], fecal calprotectin, serum analytes/micro ribonucleic acid [miRNA], whole blood gene expression/miRNA, fecal microbiota).

6. To evaluate the effect of GLPG0634 on histopathological features of the intestinal mucosa.

The following evaluations were performed:

- Simplified Endoscopy Score for CD (SES-CD) scoring during colonoscopy at baseline and Week 10. Only central reading results were used in the efficacy analysis.

- During each colonoscopy, biopsies covering 6 segments [rectum, sigmoid, left colon, transverse colon, right colon, and ileum] were obtained. Histopathology findings were scored using the D'Haens scoring system for CD by a central laboratory. The scoring system contained 8 histological variables that were scored independently, with grading from 0-3.

- CDAI scoring at baseline, Weeks 2, 4, 6, 10, 12, 16, 20, and at end of treatment (if applicable). All diary data for this assessment were collected over 7 days immediately prior to the study visit. An additional local laboratory hematocrit value was used to calculate the CDAI at Week 10 for re-randomization purposes only. The CDAI score calculation at Screening Visit 2 and Week 10 visit excluded diary data from the day prior to the colonoscopy visit (due to the bowel preparation during that day).

- Assessment of quality of life using the Inflammatory Bowel Disease Questionnaire (IBDQ) at baseline, Weeks 10, 20, and end of treatment visit (if applicable). The IBDQ is a 32-item disease-specific

questionnaire consisting of 4 domains (bowel symptoms, emotional function, social function, and systemic symptoms).

- Pharmacodynamic assessments at every visit: C-reactive protein (CRP) in serum, calprotectin levels in stool

- Blood samples were collected from subjects participating in the PK substudy, to assess the steady-state PK of filgotinib and its metabolite (G254445). Samples were collected at 0, 1, 2, 3, 5, and 8 hours post morning dose of study medication at either the Week 2 or the Week 4 visit.

- No exposure-response (E-R) modelling was performed due to the fact that only one filgotinib dose was tested versus placebo in Part 1 of the study.

- Safety evaluations were monitored in all subjects who received at least 1 dose of study medication.

Statistical Methods for the main analysis (Part 1 of the study)

The intent-to-treat [ITT] population was defined as all randomized subjects who have at least 1 dose of study drug and have at least 1 post baseline assessment of the CDAI score in the period (n=172). The Per-protocol [PP] population was a subpopulation of ITT, excluding major protocol deviations related to the first study period (n=141). The safety population was defined as all subjects randomized and exposed at least once dose (n=174).

The methods of handling missing data during the first part of the study were as follows:

- Missing data for subjects who prematurely discontinue the study during the first part were imputed for the remainder of the first part but were not imputed for the second part.

- Binary data in discontinued subjects: subjects were classified as non-responders (non-responder imputation (NRI) algorithm) for the remaining visits in the analysis period.

-Continuous data (e.g., CDAI, SES-CD, IBDQ, CDAI subscores) in discontinued subjects: a last-observation-carried-forward (LOCF) approach was used to impute missing data for the remaining visits in the analysis period.

The sample size calculation was based on the expected clinical remission rates at Week 10. Assuming 2 treatment arms with unequal 3:1 group allocation (n=135 for the filgotinib 200 mg group and n=45 for the placebo group, total n=180 subjects), a 5% 2-sided type I error and a 20% to 30% clinical remission rate for placebo, then the study has 80% power to detect a 22% to 24% treatment difference versus placebo at Week 10.

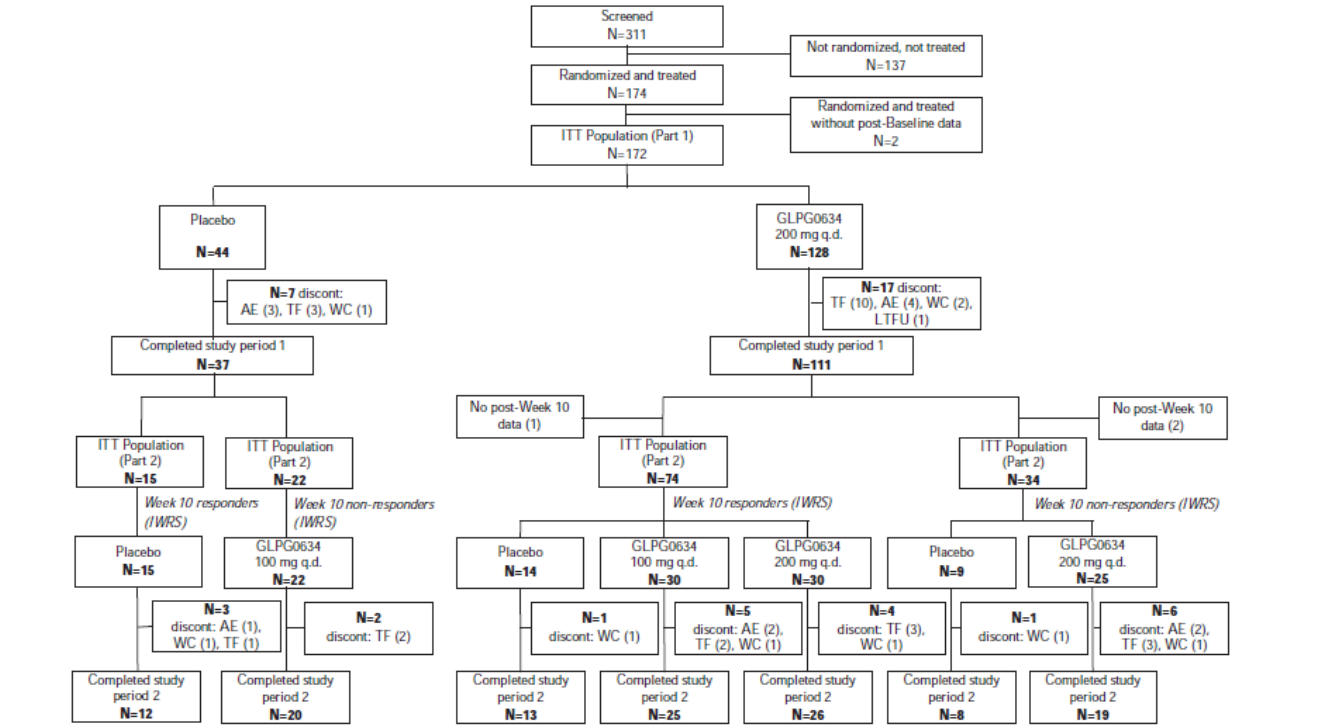
Statistical Methods for Part 2 of the study

The study was not powered for Part 2. All results (including any provided p-values) are purely descriptive. In addition, the number of subjects in the different groups was low.

Subjects disposition

A total of 311 subjects were screened and 174 subjects across 52 sites in 9 countries (Belgium, Czech Republic, France, Germany, Hungary, Poland, Romania, Russia and the UK) were randomized and treated.

A schematic overview of the subject disposition in the ITT Population for the entire study (i.e. including re-randomization based on response during Weeks 1-10) is provided in the Figure below.



AE = adverse event; discont. = discontinued; LTFU = long-term follow-up; N = number of subjects per group; TF = treatment failure; q.d. = *quaque die*, once daily; WC = withdrawal of consent

Figure 17 Study GLPG0634-CL-211 (FITZROY) Subjects disposition ITT population

Overall, a total of 148 subjects (85.1%) completed study part 1. A total of 26 subjects (14.9%) discontinued the study during the first 10 weeks of treatment. The reasons for discontinuation were treatment failure (13 subjects [7.5%]), the occurrence of AEs (7 subjects [4.0%]), subject withdrew consent (4 subjects [2.3%]), subject lost to FU and reasons listed as "other" (1 subject [0.6%] each). Overall, no relevant difference in the number of subjects who discontinued was observed between the GLPG0634 and placebo groups in the first 10 weeks of the study (refer to table below).

Table 11 Subject disposition up to week 10: reasons for study discontinuation (safety population [part 1])

	Placebo N = 44	GLPG0634 200 mg q.d. N = 130	Total N = 174
	n (%)		
Completed study part 1	37 (84.1)	111 (85.4)	148 (85.1)
Discontinued study part 1	7 (15.9)	19 (14.6)	26 (14.9)
Reasons for discontinuation			
Treatment failure	3 (6.8)	10 (7.7)	13 (7.5)
AE	3 (6.8)	4 (3.1)	7 (4.0)
Subject withdrew consent	1 (2.3)	3 (2.3)	4 (2.3)
LTFU	0	1 (0.8)	1 (0.6)
Other	0	1 (0.8)	1 (0.6)

AE = adverse event; LTFU = lost to follow-up; N = number of subjects per treatment group; n = number of subjects with event; q.d. = *quaque die*, once daily

Note: The denominator for percentage calculations was total number of subjects per treatment group in the Safety Population.

A total of 123 subjects out of 147 subjects (83.7%) who completed Part 1 and were treated in Part 2 completed study part 2. A total of 24 subjects (16.3%) discontinued the study during the second study part. The reasons for discontinuation were treatment failure (11 subjects [7.5%]), subject withdrew consent (7 subjects [4.8%]), and the occurrence of AEs (6 subjects [4.1%]) (refer to table below).

Table 12 Subject disposition up to week 10: reasons for study discontinuation (safety population [part 2])

	Continued Placebo N = 15	Placebo Switched to GLPG0634 100 mg q.d. N = 22	Continued GLPG0634 200 mg q.d. N = 57	GLPG0634 200 mg q.d. switched to 100 mg q.d. N = 30	GLPG0634 200 mg q.d. switched to placebo N = 23	Total N = 147 [a]
	n (%)					
Completed study part 2	12 (80.0)	20 (90.9)	45 (78.9)	25 (83.3)	21 (91.3)	123 (83.7)
Discontinued study part 2	3 (20.0)	2 (9.1)	12 (21.1)	5 (16.7)	2 (8.7)	24 (16.3)
Reasons for discontinuation						
Treatment failure	1 (6.7)	2 (9.1)	6 (10.5)	2 (6.7)	0	11 (7.5)
Subject withdrew consent	1 (6.7)	0	3 (5.3)	1 (3.3)	2 (8.7)	7 (4.8)
AE	1 (6.7)	0	3 (5.3)	2 (6.7)	0	6 (4.1)

[a] One subject in the GLPG0634 200 mg q.d. treatment group completed study part 1, was re-randomized into the same group, but was not exposed during study part 2, resulting in 57 subjects in the continued GLPG0634 200 mg q.d. treatment group.

AE = adverse event; N = number of subjects per treatment group; n = number of subjects with event; q.d. = *quaque die*, once daily

Note: The denominator for percentage calculations was the total number of subjects per treatment group in the Safety

At Baseline of part 1, the mean (SE) CRP was 15.61 (1.551) mg/L, the mean (SE) fecal calprotectin was 606.9 (72.95) mg/kg, the mean (SE) CDAI clinical score was 293.1 (4.13), and the mean (SE) Baseline endoscopic SES-CD score was 14.6 (0.53). The overall mean (SE) duration of CD was 8.31 (0.598) years.

At Baseline, 88 subjects (50.6%) used oral GCSs; 101 subjects (58.0%) were anti-TNF experienced non responders, 69 subjects (39.7%) were anti-TNF naïve, and 4 subjects (2.3%) were anti-TNF experienced responders.

Efficacy results in part 1 of the study

CDAI Clinical Remission at Week 10 (Primary Efficacy Endpoint)

The primary endpoint of the study was met. At Week 10, 60 of 128 subjects (46.9%) who received filgotinib 200 mg achieved clinical remission versus 10 of 44 subjects (22.7%) who received placebo (p = 0.0077). (Refer to Table below).

Sensitivity analysis (NRI-LOCF-OC [ITT Population [Part 1]] and NRI-LOCF [PP Population [Part 1]] confirmed the above results proving a negligible influence of both missing data (early discontinuations) and major protocol deviations.

Table 13 Summary and analysis of CDAI clinical remission at week 10 (NRI [ITT population [Part 1]])

	Placebo N = 44	GLPG0634 200 mg q.d. N = 128	Difference (%) (GLPG0634-placebo)
Week 10			
n (%)	10 (22.7)	60 (46.9)	24.1
Overall p-value [a]			0.0077

[a] type III p-value from a logistic regression model per time point, with factors: treatment, Baseline use of oral GCSs (yes/no), Screening CRP (≤ 10 mg/L/> 10 mg/L), and previous use of anti-TNFs (naïve/experienced)

CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; GCS = glucocorticosteroids; ITT = Intent-to-treat; N = number of subjects per treatment group; n = number of subjects with CDAI clinical remission; NRI = nonresponder imputation; q.d. = *quaque die*, once daily; TNF = tumor necrosis factor

Note: CDAI clinical remission = a CDAI score of < 150

Main efficacy secondary endpoints

● CDAI clinical remission at Week 10 by stratification factors

A statistically significant influence of anti-TNF experience on CDAI clinical remission was shown. After 10 weeks of treatment, CDAI remission was achieved by 59.6% of subjects on filgotinib 200 mg q.d. compared with 12.5% of subjects on placebo in the subgroup of anti-TNF naïve subjects; CDAI remission was achieved by 36.6% and 28.6% of subjects, respectively, in the subgroup of anti-TNF experienced subjects.

No statistically significant influence of Baseline use of oral glucocortisosteroids or Screening CRP was shown.

● CDAI 100-points clinical response

The percentage of subjects achieving CDAI 100-points clinical response in the filgotinib 200 mg q.d. group increased over time and was numerically higher in the filgotinib 200 mg q.d. group compared with the placebo group at all time points. The difference was statistically significant at Week 10 (76/128 (59.4%) versus 18/44 (40.9%), p = 0.0453).

● Total SES-CD score

The total SES-CD score (centrally read) showed a small mean decrease in the filgotinib 200 mg q.d. treatment group (-2.6 at Week 10) and the placebo group (-2.7 at Week 10); the difference was not statistically significant (p = 0.8051).

● Endoscopic remission, endoscopic response, mucosal healing

- The percentage of subjects with SES-CD endoscopic remission at Week 10 was numerically higher in the filgotinib 200 mg q.d. group compared with the placebo group (17/128 (13.3%) versus 3/44 (6.8%), p = 0.3682); however, the difference was not statistically significant.

- The percentage of subjects with SES-CD endoscopic response at Week 10 was numerically higher in the filgotinib 200 mg q.d. group compared with the placebo group (32/128 (25.0%) versus 8/44 (18.2%), p = 0.4390); however, the difference was not statistically significant.

- The percentage of subjects with SES-CD mucosal healing at Week 10 was low and similar in the filgotinib 200 mg q.d. group and the placebo group (2/128 (2.3%) versus 1/44 (2.3%), p = 0.7785).

● Total D'Haens score

The histopathology total D'Haens score showed a statistically significantly greater mean decrease in the filgotinib 200 mg q.d. treatment group (-3.5 at Week 10) compared with the placebo group (-0.6 at Week 10) (p = 0.0359).

● Total IBDQ score

The total IBDQ score improved during the 10 weeks of treatment in both the filgotinib 200 mg q.d. and placebo groups at Week 10 (+33.82 and +17.56 respectively); the increase was statistically significantly higher in the filgotinib 200 mg q.d. treatment group compared with placebo at Week 10 (p = 0.0046).

Main efficacy results in part 2 of the study

● *Clinical remission at Weeks 12, 16, and 20.*

The proportion of subjects with CDAI clinical remission slightly decreased through the end of the study in initial responders (filgotinib 200 mg q.d. or placebo) (refer to table below).

In initial filgotinib 200 mg q.d. non-responders continuing on filgotinib 200 mg q.d. and initial placebo non-responders switching to filgotinib 100 mg q.d., the proportion of subjects with CDAI clinical remission increased after Week 10. However, also in initial filgotinib 200 mg q.d. non-responders switching to placebo, an increased number of subjects achieved clinical remission at Week 20 (refer to table below).

None of the differences between active treatment and placebo at Weeks 12, 16, and 20 were statistically significant.

Table 14 Summary and analysis of CDAI clinical remission at weeks 10 and 20 for initial responders (NRI and LOCF [ITT population [part 2]])

	NRI				LOCF			
	Initial GLPG0634 200 mg q.d. Responders			Initial Placebo Responders Continuing on Placebo N = 15	Initial GLPG0634 200 mg q.d. Responders			Initial Placebo Responders Continuing on Placebo N = 15
	Switched to Placebo N = 14	Switched to GLPG0634 100 mg q.d. N = 30	Continued on GLPG0634 200 mg q.d. N = 30		Switched to Placebo N = 14	Switched to GLPG0634 100 mg q.d. N = 30	Continued on GLPG0634 200 mg q.d. N = 30	
Week 10								
n (%)	10 (71.4)	26 (86.7)	19 (63.3)	8 (53.3)	11 (78.6)	26 (86.7)	20 (66.7)	11 (73.3)
Week 20								
n (%)	10 (71.4)	18 (60.0)	15 (50.0)	9 (60.0)	11 (78.6)	19 (63.3)	17 (56.7)	10 (66.7)
Overall p-value [a]	0.4470				0.4021			
Uncorrected exploratory p-value (pairwise comparison vs. "switched to placebo") [b]		0.4517	0.2102			0.2965	0.1776	
Uncorrected exploratory p-value (pairwise comparison of 200 mg vs. 100 mg) [b]			0.5133				0.6807	

a. type III p-value from a logistic regression model per time point, with factors: treatment, Baseline use of oral GCSs (yes / no), and previous use of anti-TNFs (naïve / experienced). The continued placebo arm was not included in this model.

b. The pairwise comparisons originate from the same model, and were not corrected for multiplicity.

CDAI = Crohn's Disease Activity Index; GCS = glucocorticosteroids; ITT = Intent-to-treat; LOCF = last observation carried forward; N = number of subjects per treatment group; n = number of subjects with CDAI clinical remission; NRI = nonresponder imputation; q.d. = *quaque die*, once daily; TNF = tumor necrosis factor; vs. = versus

Note: CDAI clinical remission = a CDAI score <150

Table 15 Summary and analysis of CDAI clinical remission at weeks 10 and 20 for initial nonresponders (NRI and LOCF [ITT population [part 2]])

	NRI			LOCF		
	Initial GLPG0634 200 mg q.d. Nonresponders		Initial Placebo Nonresponders Switching to GLPG0634 100 mg q.d. N = 22	Initial GLPG0634 200 mg q.d. Nonresponders		Initial Placebo Nonresponders Switching to GLPG0634 100 mg q.d. N = 22
	GLPG0634 200 mg q.d. Switched to Placebo N = 9	Continued GLPG0634 200 mg q.d. N = 25		GLPG0634 200 mg q.d. Switched to Placebo N = 9	Continued GLPG0634 200 mg q.d. N = 25	
Week 10						
n (%)	0	4 (16.0)	2 (9.1)	0	4 (16.0)	2 (9.1)
Week 20						
n (%)	3 (33.3)	6 (24.0)	7 (31.8)	3 (33.3)	7 (28.0)	7 (31.8)
Overall p-value [a]	0.3529			0.5079		

a. type III p-value from a logistic regression model per time point, with factors: treatment, Baseline use of oral GCSs (yes / no), and previous use of anti-TNFs (naïve / experienced). The placebo-100mg arm was not included in this model.

CDAI = Crohn's Disease Activity Index; GCS = glucocorticosteroids; ITT = Intent-to-treat; N = number of subjects per treatment group; n = number of subjects with CDAI clinical remission; NRI = nonresponder imputation; q.d. = *quaque die*, once daily; TNF = tumor necrosis factor

Note: Crohn's Disease Activity Index CDAI clinical remission was defined as a CDAI score <150.

● Clinical response at Weeks 12, 16, and 20.

The proportion of subjects with CDAI 100-points clinical response slightly decreased through the end of the study in initial responders (filgotinib 200 mg q.d. or placebo) (refer to table below).

In initial filgotinib 200 mg q.d. non-responders continuing on filgotinib 200 mg q.d. and initial placebo non-responders switching to filgotinib 100 mg q.d., the proportion of subjects with CDAI 100-points clinical response remained stable or increased after Week 10. However, also in the group of initial non-responders switching to placebo, some subjects achieved these clinical response criteria at Week 20 (refer to table below).

None of the differences between active treatment and placebo at Weeks 12, 16, and 20 were statistically significant.

Table 16 Summary and analysis of CDAI 100-points clinical response at weeks 10 and 20 for initial responders (NRI and LOCF [ITT population [Part 2]])

	NRI				LOCF			
	Initial GLPG0634 200 mg q.d. Responders			Initial Placebo Responders Continuing on Placebo N = 15	Initial GLPG0634 200 mg q.d. Responders			Initial Placebo Responders Continuing on Placebo N = 15
	Switched to Placebo N = 14	Switched to GLPG0634 100 mg q.d. N = 30	Continued on GLPG0634 200 mg q.d. N = 30		Switched to Placebo N = 14	Switched to GLPG0634 100 mg q.d. N = 30	Continued on GLPG0634 200 mg q.d. N = 30	
Week 10								
n (%)	12 (85.7)	29 (96.7)	25 (83.3)	11 (73.3)	13 (92.9)	29 (96.7)	28 (93.3)	15 (100.0)
Week 20								
n (%)	11 (78.6)	22 (73.3)	20 (66.7)	10 (66.7)	12 (85.7)	24 (80.0)	23 (76.7)	13 (86.7)
Overall p-value [a]	0.7761				0.8570			
Uncorrected exploratory p-value (pairwise comparison vs. "switched to placebo") [b]		0.7341	0.4959			0.7003	0.5789	
Uncorrected exploratory p-value (pairwise comparison of 200 mg vs. 100 mg) [b]			0.6608				0.8254	

[a] type III p-value from a logistic regression model per time point, with factors: treatment, Baseline use of oral GCSs (yes / no), and previous use of anti-TNFs (naïve / experienced). The continued placebo arm was not included in this model.

[b] The pairwise comparisons originate from the same model, and were not corrected for multiplicity.

CDAI = Crohn's Disease Activity Index; GCS = glucocorticosteroids; ITT = Intent-to-treat; LOCF = last observation carried forward; N = number of subjects per treatment group; n = number of subjects with CDAI 100-points clinical response; NRI = nonresponder imputation; q.d. = *quaque die*, once daily; TNF = tumor necrosis factor; vs. = versus

Note: Crohn's Disease Activity Index 100-points clinical response was defined as a change reduction in Baseline in CDAI score of at least -100 points.

Table 17 Summary and analysis of CDAI 100-points clinical response at weeks 10 and 20 for initial nonresponders (NRI and LOCF [ITT population [Part 2]])

	NRI			LOCF		
	Initial GLPG0634 200 mg q.d. Nonresponders		Initial Placebo Nonresponders Switching to GLPG0634 100 mg q.d. N = 22	Initial GLPG0634 200 mg q.d. Nonresponders		Initial Placebo Nonresponders Switching to GLPG0634 100 mg q.d. N = 22
	GLPG0634 200 mg q.d. Switched to Placebo N = 9	Continued GLPG0634 200 mg q.d. N = 25		GLPG0634 200 mg q.d. Switched to Placebo N = 9	Continued GLPG0634 200 mg q.d. N = 25	
Week 10						
n (%)	1 (11.1)	8 (32.0)	7 (31.8)	2 (22.2)	8 (32.0)	7 (31.8)
Week 20						
n (%)	3 (33.3)	8 (32.0)	13 (59.1)	3 (33.3)	9 (36.0)	13 (59.1)
Overall p-value [a]	0.6352			0.8123		

[a] type III p-value from a logistic regression model per time point, with factors: treatment, Baseline use of oral GCSs (yes / no), and previous use of anti-TNFs (naïve / experienced). The placebo-100 mg arm was not included in this model

CDAI = Crohn's Disease Activity Index; GCS = glucocorticosteroids; ITT = Intent-to-treat; LOCF = last observation carried forward; N = number of subjects per treatment group; n = number of subjects with CDAI 100-points clinical response; NRI = nonresponder imputation; q.d. = *quaque die*, once daily; TNF = tumor necrosis factor

Note: Crohn's Disease Activity Index 100-points clinical response was defined as a reduction in Baseline in CDAI score of at least -100 points.

● Change in CDAI score at Weeks 12, 16, and 20.

- In the initial responders' population, the total CDAI score remained stable or increased slightly after Week 10, but it remained lower than Baseline at Week 20. The mean change in CDAI score between Week 10 and Week 20 was equal to:

  - Initial filgotinib 200 mg q.d. responders→placebo: - 2.0 (± 13.83)
  - Initial filgotinib 200 mg q.d. responders→ filgotinib 100 mg q.d: + 32.5 (± 17.28)
  - Initial filgotinib 200 mg q.d. responders→ filgotinib 200 mg q.d: + 31.6 (± 15.94)

- In the initial non-responders' population, the mean change in CDAI score between Week 10 and Week 20 was equal to:

  - Initial filgotinib 200 mg q.d. non-responders→ placebo: - 43.0 (± 29.02)
  - Initial filgotinib 200 mg q.d. non-responders→ filgotinib 200 mg q.d: + 16.5 (± 18.40)
  - Initial placebo non-responders→ filgotinib 100 mg q.d: -18.8 (± 28.01)

None of the differences between active treatment and placebo at Weeks 12, 16, and 20 were statistically significant.

Justification for the selection of doses for phase 2b/3 studies in UC as provided by the MAH:

In the Phase 2 study GLPG0634-CL-211 (FITZROY), the primary endpoint was met, establishing the efficacy of filgotinib 200 mg: at Week 10, 46.9% (6/128) subjects who received filgotinib 200 mg achieved clinical remission versus 22.7% (10/ 44) subjects who received placebo (p = 0.0077).

In Part 2, 31.8% (7/22) subjects, who did not achieve clinical remission at Week 10 on placebo in Part 1 and were subsequently reassigned to filgotinib 100 mg in Part 2, achieved clinical remission at Week 20. Although exploratory, the efficacy results for filgotinib 100 mg in Part 2 suggest a treatment effect of filgotinib 100 mg.

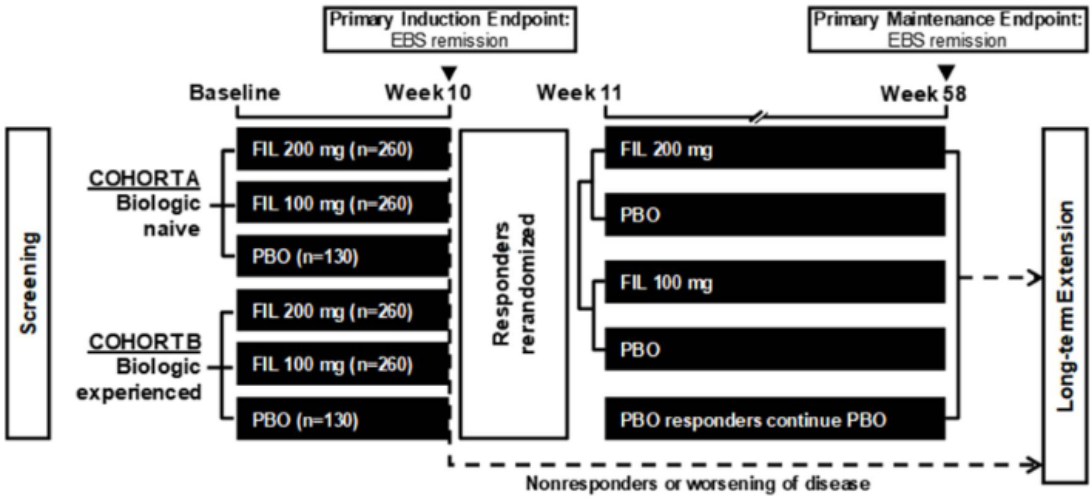
Based on the similarities in the targeted inflammatory pathways between CD and UC, existing treatment regimens for UC and CD are generally similar between the 2 conditions (e.g., infliximab, adalimumab, vedolizumab, and ustekinumab). In the absence of data from dose ranging Phase 2 studies of filgotinib in subjects with UC, the efficacy observed in subjects with CD in the exploratory 10- to 20-week arm of study GLPG0634-CL-211 supported the evaluation of the 100-mg and 200-mg once-daily dose regimens of filgotinib in study GS-US-418-3898, with an interim futility analysis for each induction study. The interim futility analysis for Study GS-US-418-3898 was performed after approximately 175 subjects completed Week 10 or discontinued from each induction study, and efficacy as assessed by endoscopic response (i.e. the proportion of subjects who achieved an endoscopic subscore of 0 or 1 for each treatment group) and overall safety were reviewed by a Data Monitoring Committee. The Cohort A Induction Study and the Cohort B Induction Study passed the predefined futility criteria and both filgotinib dose groups were evaluated for efficacy and safety in subjects with moderately to severely active UC in the induction studies and the maintenance Study.

2.4.2. Main study

Study GS-US-418-3898 (SELECTION) ***Combined Phase 2b/3, Double-Blind, Randomized, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Subjects with Moderately to Severely Active Ulcerative Colitis Methods***

Methods

The design of the pivotal Study GS-US-418-3898 is presented in the figure below.



EBS = endoscopy/bleeding/stool frequency; FIL = filgotinib; MCS = Mayo Clinic Score; PBO = placebo; TNF = tumor necrosis factor; US = United States
EBS remission, from MCS: endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and ≥ 1-point decrease in stool frequency from baseline to achieve a subscore of 0 or 1.
In the induction studies, US and Korea males who had not failed at least 2 biologic regimens (any TNF-α antagonist and vedolizumab) were randomized in a 2:1 ratio to receive either filgotinib 100 mg or placebo.
Induction responder (Week 10): achieved EBS remission or MCS response (MCS reduction ≥ 3 points and ≥ 30% from baseline, with decrease in rectal bleeding subscore of ≥ 1 or absolute rectal bleeding subscore of 0 or 1).

Figure 18 Design of the pivotal Study GS-US-418-3898

Study GS-US-418-3898 comprised the Cohort A Induction Study (biologic-naive subjects), the Cohort B Induction Study (biologic-experienced subjects), and the Maintenance Study.

In the induction studies, subjects were randomized in a 2:2:1 ratio to receive filgotinib 200 mg, filgotinib 100 mg, or placebo. Male subjects in the United States (US) and Korea who were not dual refractory (having failed any TNF-α antagonist and vedolizumab) were randomized in a 2:1 ratio to receive either filgotinib 100 mg or placebo.

Subjects in the induction studies were permitted to receive stable doses of the following: oral 5-ASA compounds, immunomodulators (azathioprine, 6-mercaptopurine [6-MP], or methotrexate [MTX]), and oral corticosteroid therapy (prednisone prescribed at a stable dose of ≤ 30 mg/day or budesonide prescribed at a stable dose of ≤ 9 mg/day).

Subjects who completed the induction studies (Day 1 to Week11) and achieved either endoscopy/bleeding/stool frequency (EBS) remission or Mayo Clinic Score (MCS) response at Week 10 were rerandomized into the Maintenance Study (Week 11 to Week 58), as follows: subjects who received filgotinib 200mg in the induction studies were randomized in a 2:1 ratio to either continue on filgotinib 200mg or switch to placebo; subjects who received filgotinib 100 mg in the induction studies were randomized in a 2:1 ratio to either continue on filgotinib 100 mg or switch to placebo; and subjects who received placebo in the induction studies continued on placebo.

Starting at Week 14, subjects who were on concomitant steroids began tapering steroid therapy.

Subjects who completed the Week 58 visit in the Maintenance Study had the option to continue study drug in a blinded fashion in an LTE study (GS-US-418-3899; study ongoing).

Subjects who did not achieve EBS remission or MCS response at Week 10 of induction treatment, or who met disease-worsening criteria in the Maintenance Study, were discontinued from blinded treatment in Study GS-US-418-3898 and had the option to receive open-label filgotinib 200 mg in StudyGS-US-418-3899, with the exception of males in the US and Korea who were not dual refractory

(having failed any TNF-α antagonist and vedolizumab); these subjects received open-label filgotinib 100 mg in Study GS-US-418-3899. After Study GS-US-418-3898 was unblinded, Study GS-US-418-3899 was also unblinded, at which point subjects who were receiving blinded placebo treatment were discontinued and subjects who were receiving blinded filgotinib treatment continued on the same dose (as received when blinded) of open-label filgotinib treatment.

Study participants

Inclusion criteria:

Subjects must have met all of the following inclusion criteria to be eligible for participation in either the Cohort A Induction Study or the Cohort B Induction Study.

1) Had the ability to understand and sign a written informed consent form, which was obtained prior to initiation of study procedures.

2) Were males or nonpregnant, nonlactating females, aged 18 to 75 years, inclusive, based on the date of the screening visit.

3) Females of childbearing potential (as defined in the clinical study protocol) must have had a negative pregnancy test at screening and baseline.

4) Male subjects and female subjects of childbearing potential who engaged in heterosexual intercourse must have agreed to use protocol-specified method(s) of contraception as described in the clinical study protocol.

5) Had a documented diagnosis of UC of at least 6 months AND with a minimum disease extent of 15 cm from the anal verge. Documentation should have included endoscopic and histopathologic evidence of UC as follows:

> a) The criteria for documentation of UC based on endoscopy was medical record documentation of, or an ileo-colonoscopy (full colonoscopy with the intubation of the terminal ileum) report dated ≥ 6 months before enrolment, which showed features consistent with UC, determined by the procedure performing physician.
>
> b) The criteria for documentation of UC based on histopathology was medical record documentation of or a histopathology report indicating features consistent with UC as determined by the pathologist.

6) A surveillance colonoscopy was required prior to screening in subjects with a history of UC for ≥ 8 years, if one was not performed in the prior 24 months.

7) Had moderately to severely active UC as determined by a centrally read endoscopy score ≥ 2, a rectal bleeding (RB)score ≥ 1, a stool frequency (SF) score ≥ 1 , and Physician's Global Assessment score of ≥ 2 as determined by the Mayo Clinic scoring system, with endoscopy occurring during screening; total score must have been between 6 and 12, inclusive.

8) Have met one of the following TB screening criteria:

> a) No evidence of active or latent TB: i) A negative Quanti-FERONTB-Gold In-Tube test (or centrally reported equivalent assay) at screening, AND ii) A chest radiograph (views as per local guidelines) taken at screening or within the 3 months prior to screening (with the report or films available for investigator review) without evidence of active or latent TB infection, AND iii) No history of either untreated or inadequately treated latent or active TB infection.

b) Previously treated for TB: i.e., if a subject had previously received an adequate course of therapy per local standard of care for either latent TB (e.g., 9 months of isoniazid in a location where rates of primary multi-drug resistant TB infections were <5% or an acceptable alternative regimen) or active TB (acceptable multi-drug regimen). In these cases, no Quanti-FERON TB-Gold In-Tube test (or centrally reported equivalent assay) needed to be obtained, but a chest radiograph was obtained if not already obtained within 3 months prior to screening (with the report or films available for investigator review). It was the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.

c) Newly identified latent TB during screening: i.e., a subject who had a newly identified positive diagnostic TB test result (defined as a positive Quanti-FERON®TB-Gold In-Tube test [or centrally reported equivalent assay]) in which active TB had been ruled out and for which appropriate, ongoing, prophylactic treatment for latent TB had been initiated for a minimum of 4weeks prior to the first administration of study medication. Adequate treatment for latent TB was defined according to local country guidelines for immunocompromised subjects. Quanti-FERON® testing was not repeated except in the case of a single repeat for indeterminate results. Cases that fell under category "b" and "c" needed to be approved by the sponsor prior to enrolment in the study. No subject with currently active TB was enrolled in the study, regardless of past or present anti-TB medication use.

9) Laboratory parameters (subjects who failed to meet the below reference laboratory tests were retested once at the discretion of investigator prior to being considered a screen failure): Hepatic panel (AST, ALT, total bilirubin) ≤ 2 ×ULN, estimated creatinine clearance(CLcr) ≥ 40 mL/min as calculated by the Cockcroft Gault equation, haemoglobin ≥ 8g/dL, absolute neutrophil count (ANC) ≥1.5 × 109/L (1500/mm3), platelets ≥ 100 × 109/L, white blood cells (WBC) ≥ 3.0 ×109/L, absolute Lymphocyte count >750/mm3.

10) May have been receiving the following drugs (subjects on these therapies were willing to remain on stable doses for the noted times):

a) Oral 5-ASA compounds provided the dose prescribed had been stable for at least 4 weeks prior to randomization; dose must have been stable for first 10 weeks after randomization.

b) Azathioprine, 6-mercaptopurine (6-MP) or methotrexate (MTX) provided the dose prescribed had been stable for 4 weeks prior to randomization; dose must have been stable for first 10 weeks after randomization.

c) Oral corticosteroid therapy (prednisone prescribed at a stable dose ≤ 30mg/day or budesonide prescribed at a stable dose of ≤ 9 mg/day) provided the dose prescribed had been stable for 2 weeks prior to randomization; dose must have been stable for first 14 weeks after randomization.

11) Were willing to refrain from live or attenuated vaccines during the study and for 12 weeks after last dose.

Exclusion criteria:

Subjects who met any of the following exclusion criteria were not enrolled in either the Cohort A Induction Study or the Cohort B Induction Study.

1) Pregnant or lactating females

2) Males and females of reproductive potential who were unwilling to abide by protocol-specified contraceptive methods as defined by the clinical study protocol

3) Females who wanted to become pregnant and/or planned to undergo egg donation or egg harvesting for the purpose of current or future fertilization during the course of the study and up to 35 days after last dose of the study drug

4) Male subjects who were unwilling to refrain from sperm donation for at least 90 days after last dose of the study drug

5) Had a known hypersensitivity to filgotinib, its metabolites, or formulation excipients

6) Exhibited acute severe UC as defined by the following criteria:

a) ≥ 6 bloody stools daily AND 1 or more of the following: i) Body temperature ≥ 100.4°F (or 38°C) ii) Pulse >90 beats per minute

7) Use of rectal formulations of 5-ASA compounds or rectal corticosteroids 2 weeks prior to screening

8) Had a history of major surgery or trauma within 30 days prior to screening

9) Presence of Crohn's disease (CD), indeterminate colitis, ischemic colitis, fulminant colitis, isolated ulcerative proctitis, or toxic mega-colon

10) Had a prior surgical intervention for UC (eg, total colectomy, subtotal colectomy, partial or hemicolectomy, ileostomy, or colostomy) or likely requirement for surgery during the study

11) Had any dependence on parenteral nutrition

12) Had a history or evidence of incompletely resected colonic mucosal dysplasia

13) Had stool sample positive for Clostridium difficile (C diff)toxin, pathogenic Escherichia coli (E coli), Salmonella species (spp), Shigellaspp, Campylobacterspp, or Yersiniaspp

14) Had stool sample positive for ova and parasites test (O&P) unless approved by the medical monitor

15) Active clinically significant infection, or any infection requiring hospitalization or treatment with intravenous anti-infectives within 30days of screening (or 8weeks of Day1); or any infection requiring oral anti-infective therapy within 2weeks of screening (or 6weeks of Day 1)

16) Infection with human immunodeficiency virus (HIV), hepatitisB virus (HBV), or hepatitisCvirus (HCV)

17) Presence of Child-Pugh Class C hepatic impairment

18) Active TB or history of latent TB that had not been treated (See inclusion criterion8 for further information)

19) Had a history of malignancy in the last 5 years except for subjects who had been successfully treated for non-melanoma skin cancer or cervical carcinoma in situ

20) Had a history of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma

21) Had a history of treatment with lymphocyte-depleting therapies, including but not limited to alemtuzumab, cyclophosphamide, total lymphoid irradiation, and rituximab

22) Had a history of cytapheresis ≤ 2 months prior to screening

23) Use of prohibited concomitant medications

24) Any chronic medical condition (including, but not limited to, cardiac or pulmonary disease, or substance abuse) or psychiatric problem that, in the opinion of the investigator or sponsor, would have

made the subject unsuitable for the study or would have prevented compliance with the study protocol procedures

25) Had administration of a live or attenuated vaccine within 30 days of randomization

26) Had a history of opportunistic infection or immunodeficiency syndrome

27) Was on any chronic systemic (oral or intravenous) anti-infective therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, atypical mycobacteria)

28) Had a history of disseminated Staphylococcus aureus

29) Had a history of symptomatic herpes zoster or herpes simplex within 12 weeks of screening, or any history of disseminated herpes simplex, disseminated herpes zoster, ophthalmic zoster, or central nervous system zoster

Additional Eligibility Criteria for Cohort A (Biologic Naive) Induction Study:

- Previously demonstrated an inadequate clinical response, loss of response to, or intolerance to at least one of the following agents (depending on current country treatment recommendations/guidelines):
    - Corticosteroids: active disease despite a history of at least an induction regimen of a dose equivalent to oral prednisone 30mg daily for 2weeks or intravenously (IV) for 1 week, or 2 failed attempts to taper steroids below a dose equivalent of 10mg daily prednisone, or a history of steroid intolerance
    - Immunomodulators: active disease despite a history of at least a 12-week regimen of oral azathioprine (≥ 2 mg/kg/day) or 6-MP (≥ 1 mg/kg/day), or MTX (25mg subcutaneously [SC] or intramuscularly [IM]per week for induction and ≥ 15mg IM per week for maintenance), or a history of intolerance to at least one immunomodulator
- No prior or current use of any TNF-α antagonist
- No prior or current use of vedolizumab at any time

Additional Eligibility Criteria for Cohort B (Biologic Experienced) Induction Study:

- Previously demonstrated an inadequate clinical response, loss of response to, or intolerance of at least one of the following agents (depending on current country treatment recommendations/guidelines):
    - TNF-α Antagonists: active disease despite a history of at least one induction regimen of a TNF-α antagonist: infliximab(minimum induction regimen of 5mg/kg at 0, 2, and 6 weeks [in the European Union (EU), duration of treatment of 14 weeks]); adalimumab (8-week induction regimen consisting of 160mg [four40-mg injections in 1day or two 40-mg injections per day for 2 consecutive days] on Day1, followed by a second dose 2 weeks later of 80mg and a 40-mg dose 2 weeks later, followed by a 40-mg dose every other week until Week8); golimumab(minimum induction duration of 6weeks [12 weeks in EU] including a 200mg SC injection at Week0, followed by 100 mg at Week 2, and then 100mg every 4 weeks), or a recurrence of symptoms during maintenance therapy with any of these agents, or a history of intolerance to any TNF-α antagonists
    - Vedolizumab: active disease despite a history of at least a 14-week (10 weeks in EU) induction regimen consisting of 300mg IV at Weeks 0, 2, and 6, or a history of intolerance to vedolizumab

- Must not have used any TNF-α antagonist or vedolizumab ≤8 weeks prior to screening or any other biologic agent ≤ 8 weeks prior to screening or within 5 times the half-life of the biologic agent prior to screening, whichever was longer

Main Eligibility Criteria for Maintenance Study:

- Subjects must have completed the Cohort A or Cohort B Induction Study with an MCS response or EBS remission based on Week10 assessments.

Treatments

Treatment Groups (Induction Studies)

- Filgotinib 200mg: filgotinib 200mg and placebo-to-match (PTM) filgotinib 100mg, once daily
- Filgotinib 100mg: filgotinib 100mg and PTM filgotinib 200mg, once daily
- Placebo: PTM filgotinib 200 mg and PTM filgotinib 100mg, once daily

Male subjects from the US and Korea who had not failed at least 2 biologic therapies (any TNF-α antagonist and vedolizumab; non-dual refractory) were randomized in a 2:1 ratio to either filgotinib 100mg or respective placebo.

Subjects from the induction studies who were eligible for the Maintenance Study were rerandomized to treatment as shown in the table below. Subjects receiving filgotinib 200mg or 100mg in the induction studies were randomized in a 2:1 manner to either continue on the assigned filgotinib regimen or to placebo for the duration of the Maintenance Study.

Table 18 GS-US-418-3898: Rerandomization for Maintenance Study

Treatment Assignment: Cohort A Induction Study and Cohort B Induction Study	Rerandomization: Maintenance Study
Filgotinib 200 mg	Filgotinib 200 mg
	Placebo
Filgotinib 100 mg	Filgotinib 100 mg
	Placebo
Placebo	Placebo

Objectives

Induction Studies: Cohort A (Biologic Naive) and Cohort B (Biologic Experienced)

The primary objective of the induction studies was as follows:

- To evaluate the efficacy of filgotinib as compared with placebo in establishing endoscopy/bleeding/stool frequency (EBS) remission at Week 10

The secondary objectives of the induction studies were as follows

- To evaluate the efficacy of filgotinib as compared with placebo in establishing Mayo Clinic Score (MCS) remission at Week 10
- To evaluate the efficacy of filgotinib as compared with placebo in establishing an endoscopic subscore of 0 at Week 10

- To evaluate the efficacy of filgotinib as compared with placebo in establishing Geboes histologic remission at Week 10
- To evaluate the efficacy of filgotinib as compared with placebo in establishing MCS remission (alternative definition) at Week 10
- To evaluate the safety and tolerability of filgotinib
- To assess the pharmacokinetic (PK) characteristics of filgotinib

Maintenance Study:

The primary objective of the Maintenance Study was as follows:

- To evaluate the efficacy of filgotinib as compared with placebo in establishing EBS remission at Week 58

The secondary objectives of the Maintenance Study were as follows:

- To evaluate the efficacy of filgotinib as compared with placebo in establishing MCS remission at Week 58
- To evaluate the efficacy of filgotinib as compared with placebo in establishing sustained EBS remission at Week 58, defined as EBS remission at Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared with placebo in establishing 6-month corticosteroid-free EBS remission at Week 58
- To evaluate the efficacy of filgotinib as compared with placebo in establishing an endoscopic subscore of 0 at Week 58
- To evaluate the efficacy of filgotinib as compared with placebo in establishing Geboes histologic remission at Week 58
- To evaluate the efficacy of filgotinib as compared with placebo in establishing MCS remission (alternative definition) at Week 58
- To evaluate the safety and tolerability of filgotinib
- To assess the PK characteristics of filgotinib

Outcomes/endpoints

Definitions of Primary, Key Secondary, and Selected Exploratory Endpoints in the **Induction Studies**

Table 19 Definitions of Primary, Key Secondary, and Selected Exploratory Endpoints in the Induction Studies

Endpoint	Definition
Primary Endpoint	
EBS Remission at Week 10	Endoscopic subscore of 0 or 1[a], RB subscore of 0, and at least a 1-point decrease in SF from baseline to achieve a subscore of 0 or 1
Key Secondary Endpoints	
MCS Remission at Week 10	MCS of 2 or less and no single subscore higher than 1
Endoscopic Subscore of 0 at Week 10	Endoscopic subscore of 0[a]
Geboes Histologic Remission at Week 10	Grade 0 of ≤ 0.3, Grade 1 of ≤ 1.1, Grade 2a of ≤ 2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0, based on the Geboes Scale
MCS Remission (Alternative Definition) at Week 10	RB, SF, and Physician's Global Assessment subscores of 0 and an endoscopic subscore of 0 or 1[a]; overall MCS of ≤ 1
Selected Exploratory Endpoints	
Endoscopic Response at Week 10	Endoscopic subscore of 0 or 1[a]
MCS Response at Week 10	MCS reduction of ≥ 3 points and at least 30% from baseline score with an accompanying decrease in RB subscore of ≥ 1 point or an absolute RB subscore of 0 or 1
EBS Remission (Alternative Definition) at Week 10	Endoscopic subscore of 0 or 1[a], RB subscore of 0, and SF subscore of 0 or 1
Change from Baseline in Partial MCS by Visit	Sum of RB, SF, and Physician's Global Assessment subscores
Change from Baseline in HRQoL at Week 10	SF-36, WPAI, EQ-5D, and IBDQ
Change from Baseline in Biomarkers by Visit	Serum hs-CRP and fecal calprotectin

EBS = endoscopy/bleeding/stool frequency; EQ-5D = EuroQoL (health-related quality of life questionnaire); HRQoL = health-related quality of life; hs-CRP = high-sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = Mayo Clinic Score; RB = rectal bleeding; SF = stool frequency; SF-36 = short-form 36 health survey; WPAI = Work Productivity and Activity Impairment

a Endoscopy assessments were centrally read.

Definitions of Primary, Key Secondary, and Selected Exploratory Endpoints in the Maintenance Study

Table 20 Definitions of Primary, Key Secondary, and Selected Exploratory Endpoints in the Maintenance Study

Endpoint	Definition
Primary Endpoint	
EBS Remission at Week 58	Endoscopic subscore of 0 or 1[a], RB subscore of 0, and at least a 1-point decrease in SF from baseline to achieve a subscore of 0 or 1
Key Secondary Endpoints	
6-month Corticosteroid-free EBS Remission[b] at Week 58	EBS remission with no corticosteroid use for the indication of UC for at least 6 months prior to Week 58 among subjects who were on corticosteroid at baseline of Maintenance Study
Sustained EBS Remission at Week 58	EBS remission at both Week 10 and Week 58
MCS Remission at Week 58	MCS of 2 or less and no single subscore higher than 1
Endoscopic Subscore of 0 at Week 58	Endoscopic subscore of 0[a]
Geboes Histologic Remission at Week 58	Grade 0 of ≤ 0.3, Grade 1 of ≤ 1.1, Grade 2a of ≤ 2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0, based on the Geboes Scale
MCS Remission (Alternative Definition) at Week 58	RB, SF, and Physician's Global Assessment subscores of 0 and an endoscopic subscore of 0 or 1[a]; overall MCS of ≤ 1
Selected Exploratory Endpoints	
Endoscopic Response at Week 58	Endoscopic subscore of 0 or 1[a]
MCS Response at Week 58	MCS reduction of ≥ 3 points and at least 30% from baseline score with an accompanying decrease in RB subscore of ≥ 1 point or an absolute RB subscore of 0 or 1
EBS Remission (Alternative Definition) at Week 58	Endoscopic subscore of 0 or 1[a], RB subscore of 0, and SF subscore of 0 or 1
Change from Baseline in Partial MCS by Visit	Sum of RB, SF, and Physician's Global Assessment subscores
Change from Baseline in HRQoL by Visit	SF-36, WPAI, EQ-5D, and IBDQ
Change from Baseline in Biomarkers by Visit	Serum hs-CRP and fecal calprotectin

EBS = endoscopy/bleeding/stool frequency; EQ-5D = EuroQoL (health-related quality of life questionnaire); HRQoL = health-related quality of life; hs-CRP = high-sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = Mayo Clinic Score; RB = rectal bleeding; SF = stool frequency; SF-36 = short-form 36 health survey; UC = ulcerative colitis; WPAI = Work Productivity and Activity Impairment

a Endoscopy assessments were centrally read.

b Subjects who tapered off steroids but required re-initiation within 6 months prior to the Week 58 assessment were considered to have not met this endpoint.

Mayo Clinic Scores (MCS):

The MCS system is a composite index of 4 disease activity variables. Each variable is scored individually on an integer scale of 0 to 3, inclusive, with higher scores indicating greater disease activity. The individual components of the MCS include stool frequency (SF), rectal bleeding (RB), endoscopic subscore, and the physician's global assessment (PGA). SF and RB are determined using an electronic daily diary, which collects subject reported components directly. The primary and key secondary efficacy endpoints, except for histologic based endpoints, are all based on the four individual components. MCS is calculated as the sum of the 4 subscores, ranging from 0 to 12. A pMCS is calculated as the sum of the 3 subscores excluding the endoscopic subscore, ranging from 0 to 9.

Table 21 Geboes Histological Score Grades

	Subgrades	Structural (Architectural Change)
Grade 0	0.0	No abnormality
	0.1	Mild abnormality
	0.2	Mild or moderate diffuse or multifocal abnormalities
	0.3	Severe diffuse or multifocal abnormalities
Grade 1		**Chronic inflammatory infiltrate**
	1.0	No increase
	1.1	Mild but unequivocal increase
	1.2	Moderate increase
	1.3	Marked increase
Grade 2		**Lamina propria neutrophils and eosinophils**
	2A Eosinophils	
	2A.0	No increase
	2A.1	Mild but unequivocal increase
	2A.2	Moderate increase
	2A.3	Marked increase
	2B Neutrophils	
	2B.0	None
	2B.1	Mild but unequivocal increase
	2B.2	Moderate increase
	2B.3	Marked increase
Grade 3		**Neutrophils in epithelium**
	3.0	None
	3.1	< 5% crypts involved
	3.2	< 50% crypts involved
	3.3	> 50% crypts involved
Grade 4		**Crypt destruction**
	4.0	None
	4.1	Probable – local excess of neutrophils in part of crypt
	4.2	Probable – marked attenuation
	4.3	Unequivocal crypt destruction
Grade 5		**Erosion or ulceration**
	5.0	No erosion, ulceration, or granulation tissue
	5.1	Recovering epithelium + adjacent inflammation
	5.2	Probable erosion – focally stripped
	5.3	Unequivocal erosion
	5.4	Ulcer or granulation tissue

SF 36

The SF-36 is a HRQoL instrument consisting of 36 questions belonging to 8 domains in 2 components and covers a 4-week recall period:

- Physical well-being, 4 domains: physical functioning (10 items), role physical (4 items), bodily pain (2 items), and general health perceptions (5 items).
- Mental well-being, 4 domains: vitality (4 items), social functioning (2 items), role emotional (3 items), and mental health (5 items). The remaining item (health transition) is not part of the above domains but is kept separately. These scales were rescaled from 0 to 100 (converting the lowest possible score to 0 and the highest possible score to 100), with higher scores indicating a better quality of life. The SF-36 is not disease specific and has been validated in numerous health states.

WPAI-Work Productivity and Activity Impairment

The WPAI is a designed to measure the effect of general health and symptom severity on work productivity and regular activities during the past 7 days. The questionnaire consists of 6 questions: Work Productivity and Activity Impairment questionnaire outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, that is, worse outcomes, as the following domains:

- The percentage of work time missed (absenteeism) due to UC: 100×Question2 / (Question2 + Question 4)
- The percentage of impairment while working (presenteeism) due to UC: 100×Question5 / 10
- The percentage of overall work impairment (work productivity loss) due to UC: 100×{Question2/ (Question2 + Question4) + [(1 − Q uestion2/(Question2 + Question4)×(Q uestion5 / 10)]}•
- The percentage of activity impairment due to UC: 100×Question 6 / 10

EQ-5D

The EQ-5D consists of 2 components: a descriptive system of the subject's health and a rating of his or her current health state using a 0 to 100 VAS. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Inflammatory Bowel Disease Questionnaire (IBDQ):

This disease-specific questionnaire comprises 32 questions divided into 4 health subscales: bowel symptoms (10 questions); systemic symptoms, including sleep disorders and fatigue (5 questions); emotional function such as depression, aggression and irritation (12 questions); and social function, meaning the ability to participate in social activities and to work (5 questions).

Sample size

Induction Studies (Cohorts A and B)

The number of subjects planned were approximately 650 subjects for each cohort, for a total of 1300 subjects. A sample size of 130 subjects in the placebo group and 260 subjects in each filgotinib dose (200 mg or 100 mg) group was expected to provide 90% power for each filgotinib dose group comparison to placebo at a 2-sided 0.025 significance level to detect a treatment difference in EBS remission rate at Week 10 of 15% (25% on filgotinib and 10% on placebo).

Maintenance Study

Assuming an induction response rate (i.e., proportion of subjects achieving either EBS remission or MCS response at Week 10) of 55% among subjects receiving filgotinib 200 mg or 100 mg treatment, approximately 285 subjects from each filgotinib dose group from Cohorts A and B Induction Studies combined would be eligible to be re-randomised into the Maintenance Study. A sample size of 95 subjects in the placebo group and 190 subjects in the filgotinib group at the same dose level as the induction dose (200 mg or 100 mg) was expected to provide more than 85% power for each filgotinib dose group comparison to placebo at a 2-sided 0.025 significance level to detect a treatment difference in maintenance EBS remission rate at Week 58 of 20% (40% on filgotinib and 20% on placebo).

Randomisation

Subjects were randomly assigned to treatment groups via an Interactive Web Response System (IWRS) using stratified randomisation schedules.

Induction studies (cohorts A and B)

Subjects who were found eligible were enrolled in Cohort A or Cohort B based on prior exposure to biologic therapy and were subsequently randomised 2:2:1 to receive filgotinib 200 mg, filgotinib 100 mg or placebo. Male subjects from the US and Korea who had not failed at least 2 biologic therapies (any TNF-α antagonist and vedolizumab; non-dual refractory) were randomised in a 2:1 ratio to either filgotinib 100 mg or respective placebo.

Within each cohort, treatment assignments were stratified according to the following factors:

Cohort A, Biologic-Naïve Induction Study

- Concomitant use of oral, systemically absorbed corticosteroids (e.g., prednisone) at Day 1, (Yes/No)
- Concomitant use of immunomodulators (e.g., 6-mercaptopurine [6-MP], azathioprine, methotrexate [MTX]) at Day 1, (Yes/No)

Cohort B, Biologic-Experienced Induction Study

- Exposure to one biologic agent versus more than one biologic agent
- Concomitant use of oral, systemically absorbed corticosteroids (e.g., prednisone) at Day 1, (Yes/No)
- Concomitant use of immunomodulators (e.g., 6-MP, azathioprine, MTX) at Day 1, (Yes/No)

Maintenance study

Re-randomisation for Maintenance Study at Week 11

Subjects in Cohorts A and B who completed the Induction Study and achieved either EBS remission or MCS response at Week 10 were re-randomised into the Maintenance Study at Week 11. Subjects receiving filgotinib 200 mg or 100 mg in the induction studies were randomised in a 2:1 manner to either continue on the assigned filgotinib regimen or to placebo for the duration of the Maintenance Study.

Table 22 Randomisation maintenance study

Treatment Assignment: Cohort A Induction Study and Cohort B Induction Study	Rerandomization: Maintenance Study
Filgotinib 200 mg	Filgotinib 200 mg
	Placebo
Filgotinib 100 mg	Filgotinib 100 mg
	Placebo
Placebo	Placebo

Stratification Factors

- Participation in Cohort A or Cohort B
- Concomitant use of oral, systemically absorbed corticosteroids (e.g., prednisone) at Day 1, (Yes/No)

- Concomitant use of immunomodulators (e.g., 6-MP, azathioprine, MTX) at Day 1, (Yes/No)

Blinding (masking)

Study GS-US-418-3898 was double-blind. Placebo-to-match (PTM) filgotinib 200 mg and 100 mg tablets were identical in appearance to the respective active tablets. Filgotinib tablets, 100 mg and 200 mg, and PTM filgotinib tablets, 100 mg and 200 mg, were administered once daily.

- Filgotinib 200 mg: filgotinib 200 mg and placebo-to-match (PTM) filgotinib 100 mg
- Filgotinib 100 mg: filgotinib 100 mg and PTM filgotinib 200 mg
- Placebo: PTM filgotinib 200 mg and PTM filgotinib 100 mg

Statistical methods

Induction Studies (Cohorts A and B) and Maintenance study

Analysis sets

The primary analysis set for efficacy analyses was the Full Analysis Set (FAS). In cohorts A and B, FAS included all randomised subjects who received at least 1 dose of study drug in the corresponding induction study (Day 1 to Week 10). In the maintenance study, FAS included all re-randomised subjects who met the protocol definition of EBS remission or MCS response at Week 10 and received at least 1 dose of study drug in the Maintenance Study (Weeks 11 to 58).

A Per-Protocol (PP) Analysis Set was defined for each induction study and the maintenance study and included a subset of subjects in the respective FAS as based on pre-defined criteria.

For analyses based on FAS, subjects were grouped according to the treatment to which they were randomised. For analyses based on e.g. the PP Analysis Sets and the Safety Analysis Sets, subjects were grouped according to actual treatment received.

Primary analysis

The primary analysis compared each filgotinib dose group to placebo on the proportion of subjects achieving EBS remission at Week 10 for Cohorts A and B and at week 58 for the Maintenance study, respectively. The Cochran-Mantel-Haenszel (CMH) approach adjusting for stratification factors was used for hypothesis testing of the primary endpoint. The stratified CMH chi-square p-value was provided for each of the comparisons. Strata with low numbers of subjects may have been aggregated for the CMH test. The 2-sided 95% CI of EBS remission rate based on normal approximation method with a continuity correction was provided for each treatment group. In addition, non-stratified risk difference estimated along with its 2-sided 95% CI using the normal approximation (i.e., the Wald method) with a continuity correction for the difference in proportions was provided. Stratification variables based on the eCRF data were used for the analysis. Subjects who did not have sufficient measurements to determine efficacy endpoints were considered failures (i.e., non-responder imputation [NRI]).

Sensitivity Analyses for the Primary Efficacy Endpoint

All the sensitivity analyses used the same statistical method that was used for the primary analysis.

Per-Protocol Analyses

Analyses were performed based on the corresponding PP Analysis Sets for the Cohort A Induction Study, Cohort B Induction Study, and the Maintenance Study.

Locally Read Endoscopic Sub Score Analyses

To evaluate the potential disparity between centrally read endoscopy scores versus locally read scores, EBS remission rates using investigator read endoscopic sub scores were analysed based on the FAS.

Missing Data Imputation Analyses

To evaluate the impact from missing data on the EBS remission rates at Week 10 and Week 58, the following missing value imputations were used:

Observed Cases Only

Observed cases were used for analysis without any imputation. Only subjects in the FAS with both baseline and Week 10 (or Week 58) data were included for analysis.

Missing = Success

Subjects in the FAS, who did not have sufficient data to decide on EBS remission status, were imputed as having achieved EBS remission.

Missing = Success for the Placebo and Missing = Failure for the Filgotinib Groups

Subjects in the FAS, who did not have sufficient data to decide on EBS remission status, were imputed as having achieved EBS remission for the placebo group and not having achieved EBS remission for the filgotinib groups.

Multiple Imputation

Subjects in the FAS, who did not have sufficient data to decide on EBS remission status at Week 10 for the induction studies or Week 58 for the Maintenance Study, were imputed using the multiple imputation procedure. A logistic regression model was used to perform the imputation with baseline values of EBS sub scores, treatment, and stratification factors as independent variables.

Analysis Excluding US/Korea Non-Dual Refractory Males (Cohort B Induction Study Only)

To evaluate the theoretical potential for non-dual refractory subjects to have better disease prognosis and a higher chance of response, a sensitivity analysis excluding US/Korea non-dual refractory males from the placebo group in the FAS was conducted using the stratified CMH test for the treatment comparison between the filgotinib 200 mg and the placebo group on EBS remission at Week 10 in the Cohort B Induction Study.

<u>Analysis of Key Secondary Efficacy Endpoints</u>

The same statistical method described for testing the primary efficacy endpoint was used for testing the key secondary efficacy endpoints.

<u>Multiple testing procedure</u>

To control a family-wise type I error rate at 5% (i.e., $\alpha = 0.05$) for each individual study, the graphical approach {Bretz 2009} to sequentially rejective multiple test procedures was implemented using a Bonferroni approach allocating 0.025 (2-sided) to each filgotinib dose group comparison with placebo. Due to an unblinded interim futility analysis planned for each induction study (Cohort A and Cohort B), an alpha of 0.00001 was spent for each filgotinib dose group comparison to placebo and therefore, a nominal p-value <0.02499 (2-sided) was needed to declare statistical significance for the final primary analysis of each filgotinib dose group when compared with placebo.

Once all hypotheses within the same filgotinib dosing regimen were rejected, then the 0.02499 alpha (within each induction study) or 0.025 (in the maintenance study) could be passed on to the other regimen's hypotheses, that is, all hypotheses in the other filgotinib dosing regimen would be tested at 2-sided 0.04998 (for the induction studies) or 2-sided 0.05 (for the maintenance study) (see figures below). If an endpoint within a filgotinib dosing regimen failed to reach statistical significance, then formal sequential testing stopped, and only nominal significance were reported for the remaining endpoints within that filgotinib dosing regimen.

Induction Studies (Cohorts A and B): *Maintenance Study:*

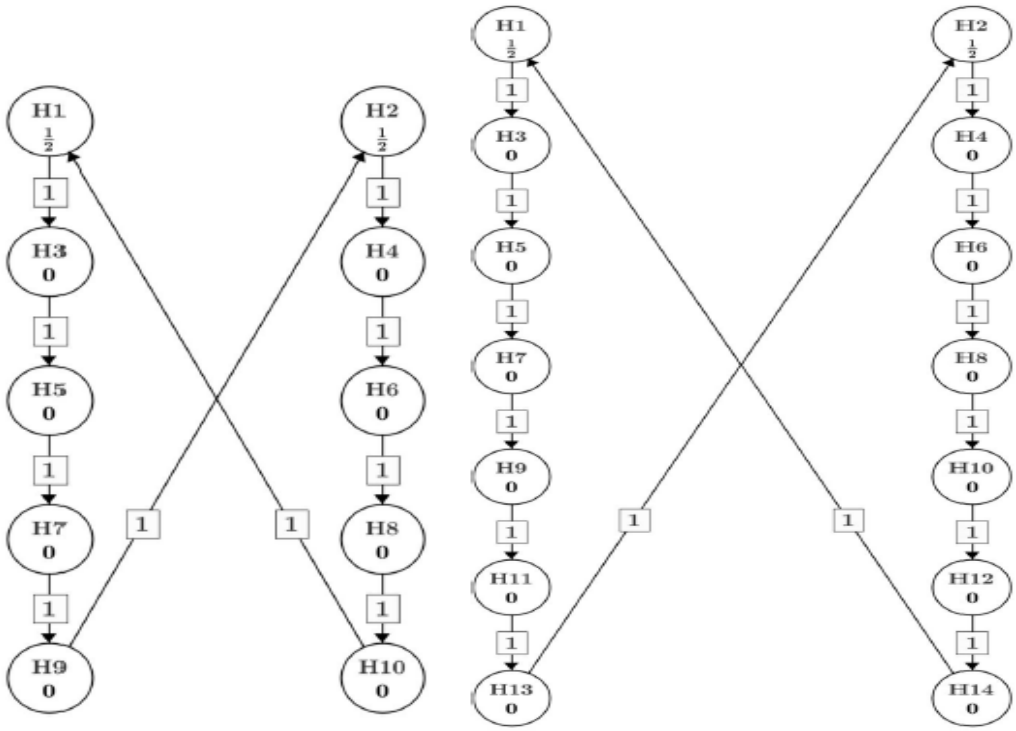


Figure 19 Testing Strategy for the Primary and Key Secondary Hypotheses

The primary statistical hypotheses at Weeks 10 and 58 were as follows:

H1: The EBS remission rate in the filgotinib 200 mg group is equal to the EBS remission rate in the placebo group.

H2: The EBS remission rate in the filgotinib 100 mg group is equal to the EBS remission rate in the placebo group.

If the primary null hypothesis was rejected, then the next key secondary hypothesis in the same filgotinib dosing regimen was tested at the same alpha level. In the induction studies there were four, and in the maintenance study there were six, key secondary endpoints included in the MTP (see the order of key secondary endpoints for the induction and maintenance studies, above).

Interim analysis

Interim Futility Analysis: Induction Studies (Cohorts A and B)

After 175 subjects (35 from placebo group and 70 from each filgotinib treatment group) had completed Week 10 assessments or discontinued from the study, a pre-planned interim futility analysis was conducted with the scope to evaluate the proportion of subjects in each treatment group who had achieved endoscopic response (endoscopic sub score of 0 or 1). The Data Monitoring Committee (DMC) could recommend terminating a filgotinib dose group or recommend stopping the study if the observed

proportion of subjects who had achieved endoscopic response in one or both filgotinib dose groups was less than that in the placebo group. To protect the integrity of the study due to the unblinded interim futility analysis planned for each induction study, an alpha of 0.00001 was to be spent for each filgotinib dose group comparison to placebo within each induction study.

DMC Cohorts A and B End-of-Induction Analysis

An end-of-induction analysis of efficacy and safety was performed when all subjects in the Cohort A Induction Study and Cohort B Induction Study completed Week 10 or discontinued from the studies. Both cohorts was to be examined independently by DMC and, taking into account data in Cohort A and Cohort B, if both dosing groups (200 mg and 100 mg) in both cohorts (independently examined) failed to reach statistical significance compared to placebo on EBS remission, the DMC could recommend overall study discontinuation.

Analysis of Exploratory Health-Related Quality of Life Endpoints

Health-related quality of life questionnaires included SF-36, WPAI, EQ-5D, and IBDQ, and were collected at baseline, Week 10, Week 26, and Week 58.

Change from baseline at Week 10 (the induction studies) and change from re-baseline at Weeks 26 and 58 (the maintenance study) of HRQoL endpoints were analysed using ANCOVA models including treatment, stratification factors and baseline/re-baseline score as covariates. In the analyses, missing values were imputed using a LOCF approach. Estimated means and differences between treatment groups were presented with 95% CIs and nominal p-values.

Subgroup Analyses

Subgroup analyses were performed for the primary efficacy endpoints for each individual study (Cohort A Induction Study, Cohort B Induction Study, and Maintenance Study).

If the value of the grouping variable could not be determined for a subject, this subject was excluded from the corresponding subgroup analysis. Non-stratified risk difference between treatment groups was evaluated for each of the subgroups using Fisher's exact test. The non-stratified risk difference and 95% CI using normal approximation with a continuity correction on the treatment differences (filgotinib − placebo) in EBS remission rates for each of the subgroups was graphically presented by Forest plot.

Changes from Planned Analyses

Protocol Amendment 5 (02 April 2019) stated that a review of the results of all primary and key secondary endpoints of the Cohort A Induction Study and Cohort B Induction Study would be performed by a Gilead executive team in parallel with the DMC's review of the end-of-induction analysis. This review by a Gilead executive team was not performed due to concerns raised by regulatory authorities during protocol review. No Gilead executive team member or GS-US-418-3898 study team member had access to any unblinded study results prior to study completion and database finalization/lock.

Table 23 Key dates relevant to the conduct of Study GS-US-418-3898.

GS-US-418-3898: Key Dates

Event	Date
First Subject Screened	14 November 2016
First Subject Enrolled (or Randomized)	7 December 2016
Interim Futility Analysis	13 April 2018
Last Subject Enrolled (or Randomized)	21 February 2019
End of Induction Study Analysis	21 June 2019
Last Subject Last Observation for the Primary Endpoint	31 March 2020
Last Subject Last Observation for this Report	31 March 2020
Database Finalization	5 May 2020
Treatment Unblinding	6 May 2020

Results

Participant flow

Subject Disposition induction studies:

Table 24 GS-US-418-3 898: Disposition of Study Subjects, Cohort A Induction Study (All Screened Subjects)

	Filgotinib 200 mg	Filgotinib 100 mg	Placebo	Total
Screened				1090
Met All Eligibility Criteria but Not Randomized				33
All Randomized Analysis Set	245	278	137	660
Safety Analysis Set	245	277	137	659
Study Drug Completion Status				
Completed Study Drug Dosing Through Week 10	237 (96.7%)	260 (93.9%)	128 (93.4%)	625 (94.8%)
Prematurely Discontinued Study Drug	8 (3.3%)	17 (6.1%)	9 (6.6%)	34 (5.2%)
Reason for Premature Discontinuation of Study Drug				
Subject Decision	4 (1.6%)	10 (3.6%)	4 (2.9%)	18 (2.7%)
Adverse Event	3 (1.2%)	5 (1.8%)	3 (2.2%)	11 (1.7%)
Lost to Follow-Up	0	1 (0.4%)	1 (0.7%)	2 (0.3%)
Protocol Violation	0	1 (0.4%)	1 (0.7%)	2 (0.3%)
Non-Compliance with Study Drug	1 (0.4%)	0	0	1 (0.2%)
Study Completion Status				
Completed Study[a]	235 (95.9%)	256 (92.4%)	127 (92.7%)	618 (93.8%)
Prematurely Discontinued Study	10 (4.1%)	21 (7.6%)	10 (7.3%)	41 (6.2%)
Reason for Premature Discontinuation of Study				
Withdrew Consent	4 (1.6%)	11 (4.0%)	4 (2.9%)	19 (2.9%)
Adverse Event	5 (2.0%)	6 (2.2%)	4 (2.9%)	15 (2.3%)
Lost to Follow-Up	0	2 (0.7%)	1 (0.7%)	3 (0.5%)
Protocol Violation	0	2 (0.7%)	1 (0.7%)	3 (0.5%)
Non-Compliance with Study Drug	1 (0.4%)	0	0	1 (0.2%)

a Defined as completion of the protocol-planned duration of the Induction Study through Week 11.
Only subjects from Safety Analysis Set were included for the study and study drug completion status summary. Percentages were calculated based on the number of subjects in the Safety Analysis Set.

Table 25 GS-US-418-3 898: Disposition of Study Subjects, Cohort B Induction Study (All Screened Subjects)

	Filgotinib 200 mg	Filgotinib 100 mg	Placebo	Total
Screened				950
Met All Eligibility Criteria but Not Randomized				30
All Randomized Analysis Set	262	286	143	691
Safety Analysis Set	262	285	142	689
Study Drug Completion Status				
Completed Study Drug Dosing Through Week 10	242 (92.4%)	265 (93.0%)	128 (90.1%)	635 (92.2%)
Prematurely Discontinued Study Drug	20 (7.6%)	20 (7.0%)	14 (9.9%)	54 (7.8%)
Reason for Premature Discontinuation of Study Drug				
Adverse Event	15 (5.7%)	14 (4.9%)	10 (7.0%)	39 (5.7%)
Subject Decision	5 (1.9%)	3 (1.1%)	3 (2.1%)	11 (1.6%)
Protocol Violation	0	1 (0.4%)	1 (0.7%)	2 (0.3%)
Investigator's Discretion	0	1 (0.4%)	0	1 (0.1%)
Pregnancy	0	1 (0.4%)	0	1 (0.1%)
Study Completion Status				
Completed Study[a]	234 (89.3%)	262 (91.9%)	127 (89.4%)	623 (90.4%)
Prematurely Discontinued Study	28 (10.7%)	23 (8.1%)	15 (10.6%)	66 (9.6%)
Reason for Premature Discontinuation of Study				
Adverse Event	18 (6.9%)	14 (4.9%)	10 (7.0%)	42 (6.1%)
Withdrew Consent	6 (2.3%)	3 (1.1%)	3 (2.1%)	12 (1.7%)
Protocol Violation	3 (1.1%)	4 (1.4%)	2 (1.4%)	9 (1.3%)
Investigator's Discretion	0	1 (0.4%)	0	1 (0.1%)
Lost to Follow-Up	1 (0.4%)	0	0	1 (0.1%)
Pregnancy	0	1 (0.4%)	0	1 (0.1%)

a Defined as completion of the protocol-planned duration of the Induction Study through Week 11. Only subjects from Safety Analysis Set were included for the study and study drug completion status summary. Percentages were calculated based on the number of subjects in the Safety Analysis Set.

Subject Disposition Maintenance study:

Table 26 GS-US-418-3898: Subject Disposition, Maintenance Study (All Subjects who Completed the Induction Studies)

	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg			Induction Placebo	
	Maintenance Filgotinib 200 mg	Maintenance Placebo	Total	Maintenance Filgotinib 100 mg	Maintenance Placebo	Total	Maintenance Placebo	Total
Completed Induction Studies								1241
All Randomized Analysis Set	202	99	301	179	91	270	93	664
Safety Analysis Set	202	99	301	179	91	270	93	664
Study Drug Completion Status								
Completed Study Drug Dosing Through Week 58	150 (74.3%)	41 (41.4%)	191 (63.5%)	104 (58.1%)	42 (46.2%)	146 (54.1%)	64 (68.8%)	401 (60.4%)
Prematurely Discontinued Study Drug	52 (25.7%)	58 (58.6%)	110 (36.5%)	75 (41.9%)	49 (53.8%)	124 (45.9%)	29 (31.2%)	263 (39.6%)
Reason for Premature Discontinuation of Study Drug								
Protocol-Specified Disease Worsening	34 (16.8%)	49 (49.5%)	83 (27.6%)	53 (29.6%)	39 (42.9%)	92 (34.1%)	21 (22.6%)	196 (29.5%)
Adverse Event	7 (3.5%)	2 (2.0%)	9 (3.0%)	10 (5.6%)	4 (4.4%)	14 (5.2%)	3 (3.2%)	26 (3.9%)
Subject Decision	4 (2.0%)	1 (1.0%)	5 (1.7%)	6 (3.4%)	3 (3.3%)	9 (3.3%)	4 (4.3%)	18 (2.7%)
Protocol Violation	5 (2.5%)	5 (5.1%)	10 (3.3%)	3 (1.7%)	0	3 (1.1%)	1 (1.1%)	14 (2.1%)
Investigator's Discretion	0	1 (1.0%)	1 (0.3%)	2 (1.1%)	0	2 (0.7%)	0	3 (0.5%)
Pregnancy	0	0	0	1 (0.6%)	2 (2.2%)	3 (1.1%)	0	3 (0.5%)
Death	2 (1.0%)	0	2 (0.7%)	0	0	0	0	2 (0.3%)
Non-Compliance with Study Drug	0	0	0	0	1 (1.1%)	1 (0.4%)	0	1 (0.2%)
Study Completion Status								
Completed Study[a]	150 (74.3%)	41 (41.4%)	191 (63.5%)	104 (58.1%)	42 (46.2%)	146 (54.1%)	64 (68.8%)	401 (60.4%)
Prematurely Discontinued Study	52 (25.7%)	58 (58.6%)	110 (36.5%)	75 (41.9%)	49 (53.8%)	124 (45.9%)	29 (31.2%)	263 (39.6%)
Reason for Premature Discontinuation of Study								
Protocol-Specified Disease Worsening	34 (16.8%)	49 (49.5%)	83 (27.6%)	53 (29.6%)	39 (42.9%)	92 (34.1%)	21 (22.6%)	196 (29.5%)
Adverse Event	7 (3.5%)	2 (2.0%)	9 (3.0%)	10 (5.6%)	4 (4.4%)	14 (5.2%)	3 (3.2%)	26 (3.9%)
Withdrew Consent	4 (2.0%)	1 (1.0%)	5 (1.7%)	6 (3.4%)	3 (3.3%)	9 (3.3%)	4 (4.3%)	18 (2.7%)
Protocol Violation	5 (2.5%)	5 (5.1%)	10 (3.3%)	3 (1.7%)	0	3 (1.1%)	1 (1.1%)	14 (2.1%)
Investigator's Discretion	0	1 (1.0%)	1 (0.3%)	2 (1.1%)	0	2 (0.7%)	0	3 (0.5%)
Pregnancy	0	0	0	1 (0.6%)	2 (2.2%)	3 (1.1%)	0	3 (0.5%)
Death	2 (1.0%)	0	2 (0.7%)	0	0	0	0	2 (0.3%)
Non-Compliance with Study Drug	0	0	0	0	1 (1.1%)	1 (0.4%)	0	1 (0.2%)

a Defined as completion of the protocol-planned duration of the Maintenance Study through Week 58.
Only subjects from Safety Analysis Set were included for the study and study drug completion status summary. Percentages were calculated based on the number of subjects in the Safety Analysis Set.

A total of 150 subjects (74.3%) in the filgotinib 200mg group completed study drug dosing through Week 58 compared with 41 subjects (41.4%) in the respective placebo group, and 104 subjects (58.1%) in the filgotinib 100mg group completed study drug dosing through Week 58 compared with 42 subjects (46.2%) in the respective placebo group. The most common reasons for discontinuation of study drug were protocol-specified disease worsening (filgotinib 200mg: 34 subjects, 16.8%; respective placebo: 49 subjects, 49.5%; filgotinib 100mg: 53 subjects, 29.6%; respective placebo: 39subjects, 42.9%) and AE (filgotinib 200mg: 7 subjects, 3.5%; respective placebo: 2 subjects, 2.0%; filgotinib 100mg: 10 subjects, 5.6%; respective placebo: 4 subjects, 4.4%)

Disease worsening: Disease worsening was based on the following criteria:

- partial MCS score (all components of MCS except for endoscopic subscore) increase of ≥ 3 points to at least 5 points from the Week 10 value on two consecutive visits, or an increase to 9 points on two consecutive visits if the Week 10 value is >6. (The disease worsening visits may include unscheduled visits (eg, a study visit followed by an unscheduled visit, or 2 sequential unscheduled visits anytime from Week 11 onward).

- Disease worsening to the extent that the subject clinically requires medications prohibited by the study (at investigator discretion, with discussion with medical monitor if feasible); these subjects do not qualify for the LTE study.

Recruitment

Study Centres: This study was conducted at 341 study centres in 40 countries: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Republic of Georgia, Republic of Korea, Romania, Russian Federation, Serbia, Singapore, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Ukraine, United Kingdom, and the United States.

Study Start Date: 14 November 2016 (First Subject Screened).

Study End Date: 31 March 2020 (Last Subject Last Observation for the Primary Endpoint).

Conduct of the study

The original protocol was dated 15 July 2016. There were 5 amendments to the protocol. Subjects were enrolled under protocol amendments 3 through 5, and prior to the study unblinding. Major changes described in the protocol amendments are summarized below:

Protocol Amendment 1 (dated 07 September2016)

- Updates were made in the text in response to US Food and Drug Administration (FDA) requests
- Updated Study Procedures Table and footnotes to reflect changes made to study visits assessments/procedures in the protocol
- Protocol GS-US-418-3899 title changed from open-label extension to LTE study
- Sections were updated with emerging relevant nonclinical and clinical data
- A novel histologic endpoint was added to account for the evolution of understanding and thinking surrounding histologic healing
- Criteria for discontinuation for febrile neutropenia, anemia, and international normalized ratio (INR) value when considering hepatic laboratory changes were added to ensure subject safety. Additional text surrounding departure from the study clarified that pregnant subjects were to discontinue the study and that early termination (ET) and post treatment visits were requested for subjects withdrawing
- An exclusion criterion of severe hepatic impairment defined by Child-Pugh Class C was added

Protocol Amendment 2 (dated 27 October 2016)

- Updates were made in the text in response to the Voluntary Harmonization Procedure (VHP) request to include MCS remission (alternative definition) as a secondary endpoint at Week 10 and Week58
- Text was updated to clarify that lymphocyte-depleting therapies and natalizumab were prohibited concomitant medications for the duration of the study
- A rationale for the exclusion of potent P- glycoprotein (P-gp) inducers was added upon VHP request

- Additional Week 26 and Week 58 electrocardiogram (ECG) procedures were added upon VHP request
- Text was added to clarify that coagulation parameters should be tested in cases where either aspartate or alanine aminotransferase (AST/ALT)was >3×upper limit of normal (ULN), to enable compliance with subject discontinuation parameters based on AST/ALT and INR.

Protocol Amendment 2.1 – Korea (drafted April 2017)

- The use of 200 mg was restricted in males in Korea to subjects who had failed 2 classes of biologic therapies (any TNF-α antagonist and vedolizumab)

Protocol Amendment 3 (dated 15 June 2017)

- Updates were made in the text in response to the South Korean Ministry of Food and Drug Safety request that the use of filgotinib 200 mg in males in Korea be limited to subjects who had failed 2 classes of biologic therapies (any TNF-α antagonist and vedolizumab)
- Guidance from investigators regarding rate of steroid tapering was added to text and clarity was added regarding handling of subjects who exceed baseline steroid doses
- Sections were updated with emerging relevant clinical and pipeline data
- Text was updated to reflect that subjects were up to date on colorectal cancer surveillance processes prior to entering the screening period
- Text was added to clarify the type of colectomies that were excluded
- Clarity around tuberculosis (TB) eligibility was added
- Instructions for recording the Normal Stool Count and ensuring eligibility prior to endoscopy were added

Protocol Amendment 4 (dated 05 March 2018)

- The number of sites was increased to ensure that a target number of subjects were enrolled in the study considering the accumulated enrolment rate
- Provided additional clarity on inclusion/exclusion criteria including those for hepatitis
- Provided additional flexibility for enhanced safety monitoring (with increased flexibility for data monitoring committee [DMC] meeting scheduling and suggested infectious workups for disease worsening)

Protocol Amendment 5 (dated 02 April 2019)

- Removed plans for interim unblinded analysis for a prespecified sponsor's executive team review

Protocol Amendment 5.1 – Voluntary Harmonization Procedure (dated 02 August 2019)

- Sections that specified plans for interim unblinded analysis for a prespecified sponsor's executive team review were removed

Protocol Deviations

Cohort A Induction Study: A total of 135 subjects (20.5%) had at least 1 important protocol deviation (IPD) during the study. The most common IPD classification was eligibility criteria violation (75 subjects, 11.4%). The most common eligibility violations were stool samples positive for ova and parasites (25 subjects, 3.8%) and use of prohibited medications (15 subjects, 2.3%). Protocol

deviations were proportionately distributed across treatment groups. None of these IPDs affected the overall quality or interpretation of the study data.

After database lock, the study ePRO vendor ERT Health Care Company identified diary data from one Subject that were not available when the database was locked at study completion. These diary entries for RB and SF sub scores did not fall into the SAP-defined analysis calculation window for baseline MCS and therefore the omission of these diary entries had no impact on data analysis. This omission was not categorized as an IPD according to the prespecified IPD plan.

Cohort B Induction Study: A total of 231 subjects (33.4%) had at least 1 IPD during the study. The most common IPD classification was eligibility criteria violation (149 subjects, 21.6%). The most common eligibility violations were use of prohibited medications (51 subjects, 7.4%) and stool samples positive for ova and parasites (38 subjects, 5.5%). Protocol deviations were proportionately distributed across treatment groups. None of these IPDs affected the overall quality or interpretation of the study data. After database lock, the study ePRO vendor ERT Health Care Company identified diary data from one Subject that were not available when the database was locked at study completion. This subject was a screen failure and therefore the omission of these diary entries had no impact on data analysis. This omission was not categorized as an IPD according to the prespecified IPD plan

Maintenance Study: A total of 65 subjects (9.8 %) had at least 1 IPD during the study. The most common IPD classification was missing data (24 subjects, 3.6%). Protocol deviations were proportionately distributed across treatment groups. None of these IPDs affected the overall quality or interpretation of the study data.

Compliance

Treatment Compliance – Cohort A Induction Study: The mean on-treatment adherence rates to study drugs were similar across treatment groups, and over 98% of subjects in all treatment groups had on-treatment adherence rates of ≥ 80% throughout the course of the study.

Treatment Compliance – Cohort B Induction Study: The mean on-treatment adherence rates to study drugs were similar across treatment groups, and over 98% of subjects in all treatment groups had on-treatment adherence rates of ≥ 80% throughout the course of the study.

Treatment Compliance – Maintenance Study: The mean on-treatment adherence rates to study drugs were similar across treatment groups, and over 97% of subjects in all treatment groups had on-treatment adherence rates of ≥ 80% throughout the course of the study.

Baseline data

Cohort A induction study (biologic -naïve patients)

Demographics and baseline disease characteristics for subjects in the Cohort A Induction Study are summarized in the tables below.

Table 27 GS-US-418-3898: Demographics and Other Baseline Characteristics, Cohort A Induction Study (Safety Analysis Set)

	Filgotinib 200 mg (N=245)	Filgotinib 100 mg (N=277)	Placebo (N=137)	Total (N=659)
Age (years)				
N	245	277	137	659
Mean (SD)	42 (13.1)	42 (13.3)	41 (12.9)	42 (13.1)
Median	42	42	39	41
Q1, Q3	33, 53	31, 53	32, 52	32, 52
Min, Max	18, 72	18, 73	19, 72	18, 73
Age Group				
< 65 years	234 (95.5%)	261 (94.2%)	129 (94.2%)	624 (94.7%)
≥ 65 years	11 (4.5%)	16 (5.8%)	8 (5.8%)	35 (5.3%)
Sex at Birth				
Male	123 (50.2%)	157 (56.7%)	87 (63.5%)	367 (55.7%)
Female	122 (49.8%)	120 (43.3%)	50 (36.5%)	292 (44.3%)
Race				
American Indian or Alaska Native	1 (0.4%)	0	0	1 (0.2%)
Asian	77 (31.4%)	79 (28.5%)	38 (27.7%)	194 (29.4%)
Black or African American	2 (0.8%)	3 (1.1%)	1 (0.7%)	6 (0.9%)
Native Hawaiian or Pacific Islander	0	0	0	0
White	165 (67.3%)	192 (69.3%)	95 (69.3%)	452 (68.6%)
Other	0	2 (0.7%)	2 (1.5%)	4 (0.6%)
Not Permitted	0	1 (0.4%)	1 (0.7%)	2 (0.3%)

	Filgotinib 200 mg (N=245)	Filgotinib 100 mg (N=277)	Placebo (N=137)	Total (N=659)
Ethnicity				
Not Hispanic or Latino	238 (97.1%)	269 (97.1%)	134 (97.8%)	641 (97.3%)
Hispanic or Latino	6 (2.4%)	6 (2.2%)	3 (2.2%)	15 (2.3%)
Not Permitted	1 (0.4%)	2 (0.7%)	0	3 (0.5%)
Geographic Region				
United States [US]	14 (5.7%)	33 (11.9%)	19 (13.9%)	66 (10.0%)
Non-US	231 (94.3%)	244 (88.1%)	118 (86.1%)	593 (90.0%)
Weight (kg)				
N	245	277	137	659
Mean (SD)	70.1 (17.89)	69.6 (17.69)	69.5 (15.89)	69.7 (17.39)
Median	66.2	66.8	66.5	66.2
Q1, Q3	57.0, 81.0	56.9, 81.0	58.0, 80.5	57.0, 81.0
Min, Max	36.9, 140.1	36.2, 163.6	41.8, 123.7	36.2, 163.6
Height (cm)				
N	245	277	137	659
Mean (SD)	168.4 (10.08)	168.8 (9.73)	169.6 (9.88)	168.8 (9.89)
Median	168.0	169.0	170.0	168.8
Q1, Q3	161.0, 176.0	162.0, 176.0	164.0, 178.0	162.0, 176.0
Min, Max	143.0, 200.0	140.0, 198.0	142.0, 190.0	140.0, 200.0
Body Mass Index (kg/m^2)				
N	245	277	137	659
Mean (SD)	24.7 (5.82)	24.2 (4.91)	24.0 (4.31)	24.3 (5.16)
Median	23.9	23.6	23.2	23.8
Q1, Q3	20.4, 27.9	20.6, 27.4	20.8, 26.8	20.5, 27.5
Min, Max	14.3, 53.0	13.7, 46.3	16.3, 37.7	13.7, 53.0
Smoking Status				
Former	55 (22.4%)	54 (19.5%)	22 (16.1%)	131 (19.9%)
Current	15 (6.1%)	10 (3.6%)	5 (3.6%)	30 (4.6%)
Never	175 (71.4%)	213 (76.9%)	110 (80.3%)	498 (75.6%)

Max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; US = United States
Percentages were calculated based on the number of subjects in the Safety Analysis Set. Age (in years) was calculated from date of first study drug dosing in the Cohort A Induction Study. Not Permitted = local regulators did not allow collection of race or ethnicity information. Body Mass Index (kg/m^2) = [Weight (kg) / Height $(cm)^2$] × 10,000.

Table 28 GS-US-418-3898: Baseline Disease Characteristics, Cohort A Induction Study (Safety Analysis Set

	Filgotinib 200 mg (N=245)	Filgotinib 100 mg (N=277)	Placebo (N=137)	Total (N=659)
Duration of Ulcerative Colitis (UC, years)				
N	245	277	137	659
Mean (SD)	7.2 (6.87)	6.7 (7.41)	6.4 (7.39)	6.8 (7.20)
Median	4.2	3.9	3.6	4.0
Q1, Q3	1.8, 10.3	1.7, 9.5	1.5, 8.6	1.7, 9.7
Min, Max	0.5, 36.7	0.5, 48.9	0.5, 38.9	0.5, 48.9
Mayo Clinic Score				
N	245	277	137	659
Mean (SD)	8.6 (1.31)	8.6 (1.43)	8.7 (1.32)	8.6 (1.36)
Median	9.0	9.0	9.0	9.0
Q1, Q3	8.0, 10.0	8.0, 10.0	8.0, 10.0	8.0, 10.0
Min, Max	6.0, 12.0	6.0, 12.0	6.0, 12.0	6.0, 12.0
Mayo Clinic Score Group				
≤ 8	116 (47.3%)	133 (48.0%)	65 (47.4%)	314 (47.6%)
≥ 9	129 (52.7%)	144 (52.0%)	72 (52.6%)	345 (52.4%)
Partial Mayo Clinic Score				
N	245	277	137	659
Mean (SD)	6.0 (1.24)	5.9 (1.31)	6.1 (1.29)	6.0 (1.28)
Median	6.0	6.0	6.0	6.0
Q1, Q3	5.0, 7.0	5.0, 7.0	5.0, 7.0	5.0, 7.0
Min, Max	1.0, 9.0	2.0, 9.0	3.0, 9.0	1.0, 9.0
Endoscopy Subscore (Central Read) of 3				
Yes	133 (54.3%)	159 (57.4%)	76 (55.5%)	368 (55.8%)
No	112 (45.7%)	118 (42.6%)	61 (44.5%)	291 (44.2%)

	Filgotinib 200 mg (N=245)	Filgotinib 100 mg (N=277)	Placebo (N=137)	Total (N=659)
Fecal Calprotectin (µg/g)				
N	240	272	135	647
Mean (SD)	2059 (2639.1)	2001 (3447.8)	2231 (2916.9)	2070 (3055.5)
Median	1101	1081	1528	1186
Q1, Q3	414, 2522	357, 1823	409, 2901	389, 2476
Min, Max	29, 16818	29, 28788	29, 19281	29, 28788
Fecal Calprotectin Group				
≤ 250 µg/g	35 (14.3%)	49 (17.7%)	25 (18.2%)	109 (16.5%)
> 250 µg/g	205 (83.7%)	223 (80.5%)	110 (80.3%)	538 (81.6%)
Missing	5 (2.0%)	5 (1.8%)	2 (1.5%)	12 (1.8%)
C-Reactive Protein (hs-CRP, mg/L)				
N	245	277	137	659
Mean (SD)	8.63 (16.274)	7.75 (17.384)	5.82 (7.600)	7.67 (15.426)
Median	3.57	2.43	2.78	3.03
Q1, Q3	1.42, 8.53	1.17, 7.02	1.05, 6.72	1.17, 7.71
Min, Max	0.19, 194.00	0.19, 141.00	0.19, 39.40	0.19, 194.00
C-Reactive Protein Group				
≤ 3 mg/L	111 (45.3%)	147 (53.1%)	71 (51.8%)	329 (49.9%)
> 3 mg/L	134 (54.7%)	130 (46.9%)	66 (48.2%)	330 (50.1%)
Corticosteroid and Immunomodulator Treatment at Induction Baseline				
Concomitant Use of Systemically Absorbed Corticosteroids and Immunomodulators				
Systemic Corticosteroids Only	54 (22.0%)	67 (24.2%)	34 (24.8%)	155 (23.5%)
Immunomodulators Only	53 (21.6%)	63 (22.7%)	33 (24.1%)	149 (22.6%)
Both Systemic Corticosteroids and Immunomodulators	20 (8.2%)	19 (6.9%)	8 (5.8%)	47 (7.1%)
Neither Systemic Corticosteroids nor Immunomodulators	118 (48.2%)	128 (46.2%)	62 (45.3%)	308 (46.7%)
Systemically Absorbed Corticosteroids				
Yes	74 (30.2%)	86 (31.0%)	42 (30.7%)	202 (30.7%)

	Filgotinib 200 mg (N=245)	Filgotinib 100 mg (N=277)	Placebo (N=137)	Total (N=659)
Prednisone Equivalence Dose in mg/day				
N	74	86	42	202
Mean (SD)	18.4 (9.02)	16.9 (8.95)	20.3 (8.56)	18.2 (8.94)
Median	20.0	15.0	20.0	20.0
Q1, Q3	10.0, 25.0	10.0, 25.0	15.0, 30.0	10.0, 25.0
Min, Max	2.5, 30.0	2.5, 30.0	2.5, 30.0	2.5, 30.0
Prednisone Equivalence Dose Group				
> 0 and ≤ 10 mg/day	25 (10.2%)	36 (13.0%)	10 (7.3%)	71 (10.8%)
> 10 and ≤ 20 mg/day	24 (9.8%)	27 (9.7%)	14 (10.2%)	65 (9.9%)
> 20 mg/day	25 (10.2%)	23 (8.3%)	18 (13.1%)	66 (10.0%)
No	171 (69.8%)	191 (69.0%)	95 (69.3%)	457 (69.3%)

Max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation
Percentages were calculated based on the number of subjects in the Safety Analysis Set. For use of systemic corticosteroids, only records with routes of oral, intravenous, and intramuscular were included.

Cohort B induction study (biologic -experienced patients)

Demographics and baseline disease characteristics for subjects in the Cohort B Induction Study are summarized in tables below.

Table 29 GS-US-418-3898: Demographics and Other Baseline Characteristics, Cohort B Induction Study (Safety Analysis Set)

	Filgotinib 200 mg (N=262)	Filgotinib 100 mg (N=285)	Placebo (N=142)	Total (N=689)
Age (years)				
N	262	285	142	689
Mean (SD)	43 (14.2)	43 (14.3)	44 (14.9)	43 (14.4)
Median	44	42	45	43
Q1, Q3	31, 54	31, 54	32, 55	31, 54
Min, Max	18, 72	18, 73	18, 74	18, 74
Age Group				
< 65 years	243 (92.7%)	264 (92.6%)	128 (90.1%)	635 (92.2%)
≥ 65 years	19 (7.3%)	21 (7.4%)	14 (9.9%)	54 (7.8%)
Sex at Birth				
Male	148 (56.5%)	186 (65.3%)	86 (60.6%)	420 (61.0%)
Female	114 (43.5%)	99 (34.7%)	56 (39.4%)	269 (39.0%)
Race				
American Indian or Alaska Native	0	0	0	0
Asian	50 (19.1%)	51 (17.9%)	27 (19.0%)	128 (18.6%)
Black or African American	4 (1.5%)	6 (2.1%)	3 (2.1%)	13 (1.9%)
Native Hawaiian or Pacific Islander	0	0	0	0
White	190 (72.5%)	212 (74.4%)	98 (69.0%)	500 (72.6%)
Other	0	0	1 (0.7%)	1 (0.1%)
Not Permitted	18 (6.9%)	16 (5.6%)	13 (9.2%)	47 (6.8%)
Ethnicity				
Not Hispanic or Latino	249 (95.0%)	273 (95.8%)	134 (94.4%)	656 (95.2%)
Hispanic or Latino	8 (3.1%)	8 (2.8%)	4 (2.8%)	20 (2.9%)
Not Permitted	5 (1.9%)	4 (1.4%)	4 (2.8%)	13 (1.9%)
Geographic Region				
United States [US]	36 (13.7%)	58 (20.4%)	21 (14.8%)	115 (16.7%)
Non-US	226 (86.3%)	227 (79.6%)	121 (85.2%)	574 (83.3%)
Weight (kg)				
N	262	285	142	689
Mean (SD)	73.1 (18.68)	74.7 (17.01)	73.1 (16.74)	73.8 (17.61)
Median	70.9	72.5	71.3	72.0
Q1, Q3	60.3, 84.1	62.5, 84.0	60.0, 85.0	61.3, 84.5
Min, Max	37.7, 156.8	42.0, 147.3	39.8, 139.0	37.7, 156.8

	Filgotinib 200 mg (N=262)	Filgotinib 100 mg (N=285)	Placebo (N=142)	Total (N=689)
Height (cm)				
N	262	284	142	688
Mean (SD)	170.1 (9.78)	172.3 (8.41)	171.8 (9.62)	171.3 (9.25)
Median	169.9	173.0	172.0	171.0
Q1, Q3	164.0, 177.0	167.3, 178.0	166.0, 178.0	165.0, 178.0
Min, Max	130.0, 195.0	148.3, 195.6	139.0, 198.0	130.0, 198.0
Body Mass Index (kg/m^2)				
N	262	284	142	688
Mean (SD)	25.1 (5.70)	25.0 (4.90)	24.7 (5.28)	25.0 (5.29)
Median	24.3	24.4	24.0	24.4
Q1, Q3	21.2, 28.0	21.9, 27.5	21.1, 28.3	21.3, 27.7
Min, Max	14.1, 57.6	16.4, 44.7	13.8, 48.2	13.8, 57.6
Smoking Status				
Former	73 (27.9%)	93 (32.6%)	43 (30.3%)	209 (30.3%)
Current	8 (3.1%)	21 (7.4%)	5 (3.5%)	34 (4.9%)
Never	181 (69.1%)	171 (60.0%)	94 (66.2%)	446 (64.7%)

Max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; US = United States
Percentages were calculated based on the number of subjects in the Safety Analysis Set. Age (in years) was calculated from date of first study drug dosing in Cohort B Induction Study. Not Permitted = local regulators did not allow collection of race or ethnicity information. Body Mass Index (kg/m^2) = [Weight (kg) / Height (cm)^2] × 10,000.

Table 30 GS-US-418-3898: Baseline Disease Characteristics, Cohort B Induction Study (Safety Analysis Set)

	Filgotinib 200 mg (N=262)	Filgotinib 100 mg (N=285)	Placebo (N=142)	Total (N=689)
Duration of Ulcerative Colitis (UC, years)				
N	262	284	142	688
Mean (SD)	9.8 (7.64)	9.7 (7.15)	10.2 (8.22)	9.8 (7.56)
Median	7.2	7.5	7.2	7.4
Q1, Q3	4.0, 14.1	4.3, 13.2	4.1, 13.8	4.1, 13.7
Min, Max	0.8, 34.7	0.6, 36.0	0.6, 39.7	0.6, 39.7
Mayo Clinic Score				
N	262	285	142	689
Mean (SD)	9.2 (1.39)	9.3 (1.27)	9.3 (1.42)	9.3 (1.35)
Median	9.0	9.0	9.0	9.0
Q1, Q3	8.0, 10.0	9.0, 10.0	8.0, 10.0	8.0, 10.0
Min, Max	6.0, 12.0	6.0, 12.0	6.0, 12.0	6.0, 12.0
Mayo Clinic Score Group				
≤ 8	71 (27.1%)	68 (23.9%)	42 (29.6%)	181 (26.3%)
≥ 9	191 (72.9%)	217 (76.1%)	100 (70.4%)	508 (73.7%)
Partial Mayo Clinic Score				
N	262	285	142	689
Mean (SD)	6.5 (1.38)	6.4 (1.26)	6.4 (1.40)	6.4 (1.33)
Median	7.0	6.0	6.5	7.0
Q1, Q3	6.0, 7.0	6.0, 7.0	5.0, 7.0	6.0, 7.0
Min, Max	2.0, 9.0	2.0, 9.0	2.0, 9.0	2.0, 9.0
Endoscopy Subscore (Central Read) of 3				
Yes	203 (77.5%)	222 (77.9%)	111 (78.2%)	536 (77.8%)
No	59 (22.5%)	63 (22.1%)	31 (21.8%)	153 (22.2%)
Fecal Calprotectin (µg/g)				
N	254	278	139	671
Mean (SD)	2845 (4076.5)	2236 (3094.9)	2479 (3571.4)	2517 (3596.7)
Median	1513	1378	1534	1461
Q1, Q3	584, 3217	553, 2477	685, 2866	591, 2884
Min, Max	29, 28801	29, 21690	40, 28801	29, 28801
Fecal Calprotectin Group				
≤ 250 µg/g	32 (12.2%)	35 (12.3%)	14 (9.9%)	81 (11.8%)
> 250 µg/g	222 (84.7%)	243 (85.3%)	125 (88.0%)	590 (85.6%)
Missing	8 (3.1%)	7 (2.5%)	3 (2.1%)	18 (2.6%)
C-Reactive Protein (hs-CRP, mg/L)				
N	262	285	142	689
Mean (SD)	12.21 (14.850)	11.72 (17.986)	13.98 (24.280)	12.37 (18.405)
Median	5.91	5.92	6.57	5.94
Q1, Q3	2.37, 17.40	2.38, 14.10	2.73, 17.40	2.54, 16.00
Min, Max	0.19, 78.80	0.19, 147.00	0.19, 239.00	0.19, 239.00

	Filgotinib 200 mg (N=262)	Filgotinib 100 mg (N=285)	Placebo (N=142)	Total (N=689)
C-Reactive Protein Group				
≤ 3 mg/L	77 (29.4%)	86 (30.2%)	41 (28.9%)	204 (29.6%)
> 3 mg/L	185 (70.6%)	199 (69.8%)	101 (71.1%)	485 (70.4%)
Treatment History Prior to Induction Baseline				
Number of Prior Biologic Agents Used				
0	3 (1.1%)	2 (0.7%)	3 (2.1%)	8 (1.2%)
1	80 (30.5%)	98 (34.4%)	46 (32.4%)	224 (32.5%)
2	90 (34.4%)	109 (38.2%)	45 (31.7%)	244 (35.4%)
≥ 3	89 (34.0%)	76 (26.7%)	48 (33.8%)	213 (30.9%)
Prior Use of TNF-alpha Antagonist				
Yes	242 (92.4%)	266 (93.3%)	130 (91.5%)	638 (92.6%)
Number of Prior TNF-alpha Antagonists Used				
1	126 (48.1%)	136 (47.7%)	66 (46.5%)	328 (47.6%)
2	90 (34.4%)	117 (41.1%)	54 (38.0%)	261 (37.9%)
≥ 3	26 (9.9%)	13 (4.6%)	10 (7.0%)	49 (7.1%)
Worst Outcome of Prior TNF-alpha Antagonist Use				
Treatment Failure	218 (83.2%)	251 (88.1%)	120 (84.5%)	589 (85.5%)
Intolerance (allergic and non-allergic)	16 (6.1%)	12 (4.2%)	9 (6.3%)	37 (5.4%)
Other	8 (3.1%)	3 (1.1%)	1 (0.7%)	12 (1.7%)
No	20 (7.6%)	19 (6.7%)	12 (8.5%)	51 (7.4%)
Prior Use of Vedolizumab				
Yes	164 (62.6%)	145 (50.9%)	85 (59.9%)	394 (57.2%)
Worst Outcome of Prior Vedolizumab Use				
Treatment Failure	148 (56.5%)	132 (46.3%)	76 (53.5%)	356 (51.7%)
Intolerance (allergic and non-allergic)	11 (4.2%)	9 (3.2%)	2 (1.4%)	22 (3.2%)
Other	5 (1.9%)	4 (1.4%)	7 (4.9%)	16 (2.3%)
No	98 (37.4%)	140 (49.1%)	57 (40.1%)	295 (42.8%)
Prior Use of both TNF-alpha Antagonist and Vedolizumab				
Yes	147 (56.1%)	128 (44.9%)	76 (53.5%)	351 (50.9%)
No	115 (43.9%)	157 (55.1%)	66 (46.5%)	338 (49.1%)
Prior Failure of both TNF-alpha Antagonist and Vedolizumab				
Yes (Dual Refractory)	120 (45.8%)	113 (39.6%)	64 (45.1%)	297 (43.1%)
US/Korea Males	15 (5.7%)	10 (3.5%)	5 (3.5%)	30 (4.4%)
Subjects Other than US/Korea Males	105 (40.1%)	103 (36.1%)	59 (41.5%)	267 (38.8%)
No	142 (54.2%)	172 (60.4%)	78 (54.9%)	392 (56.9%)
US/Korea Males	1 (0.4%)	30 (10.5%)	14 (9.9%)	45 (6.5%)
Subjects Other than US/Korea Males	141 (53.8%)	142 (49.8%)	64 (45.1%)	347 (50.4%)
Corticosteroid and Immunomodulator Treatment at Induction Baseline				
Concomitant Use of Systemically Absorbed Corticosteroids and Immunomodulator				
Systemic Corticosteroids Only	94 (35.9%)	103 (36.1%)	51 (35.9%)	248 (36.0%)
Immunomodulators Only	34 (13.0%)	34 (11.9%)	21 (14.8%)	89 (12.9%)
Both Systemic Corticosteroids and Immunomodulators	28 (10.7%)	28 (9.8%)	11 (7.7%)	67 (9.7%)
Neither Systemic Corticosteroids nor Immunomodulators	106 (40.5%)	120 (42.1%)	59 (41.5%)	285 (41.4%)
Systemically Absorbed Corticosteroids				
Yes	122 (46.6%)	131 (46.0%)	62 (43.7%)	315 (45.7%)

	Filgotinib 200 mg (N=262)	Filgotinib 100 mg (N=285)	Placebo (N=142)	Total (N=689)
Prednisone Equivalence Dose in mg/day				
N	122	131	62	315
Mean (SD)	16.0 (8.16)	17.3 (7.60)	16.7 (8.48)	16.7 (7.99)
Median	15.0	20.0	20.0	20.0
Q1, Q3	10.0, 20.0	10.0, 20.0	10.0, 20.0	10.0, 20.0
Min, Max	1.0, 40.0	2.0, 30.0	1.0, 30.0	1.0, 40.0
Prednisone Equivalence Dose Group				
> 0 and ≤ 10 mg/day	48 (18.3%)	40 (14.0%)	23 (16.2%)	111 (16.1%)
> 10 and ≤ 20 mg/day	53 (20.2%)	68 (23.9%)	26 (18.3%)	147 (21.3%)
> 20 mg/day	21 (8.0%)	23 (8.1%)	13 (9.2%)	57 (8.3%)
No	140 (53.4%)	154 (54.0%)	80 (56.3%)	374 (54.3%)

Max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; TNF = tumor necrosis factor; US = United States
Percentages were calculated based on the number of subjects in the Safety Analysis Set. Number of prior use of biologic agents was based on biologics approved for ulcerative colitis only. For use of systemic corticosteroids, only records with routes of oral, intravenous, and intramuscular were included.

Maintenance study

Table 31 GS-US-418-3898: Demographics and Other Baseline Characteristics, Maintenance Study (Safety Analysis Set)

	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg			Induction Placebo	
	Maintenance Filgotinib 200 mg (N=202)	Maintenance Placebo (N=99)	Total (N=301)	Maintenance Filgotinib 100 mg (N=179)	Maintenance Placebo (N=91)	Total (N=270)	Maintenance Placebo (N=93)	Overall Total (N=664)
Age (years)								
N	202	99	301	179	91	270	93	664
Mean (SD)	43 (13.8)	42 (13.0)	43 (13.5)	42 (12.6)	43 (15.1)	42 (13.5)	43 (13.0)	43 (13.4)
Median	42	42	42	42	42	42	41	42
Q1, Q3	32, 54	32, 53	32, 53	31, 53	29, 57	30, 54	32, 53	32, 53
Min, Max	18, 72	18, 71	18, 72	18, 68	19, 73	18, 73	21, 72	18, 73
Age Group								
< 65 years	187 (92.6%)	95 (96.0%)	282 (93.7%)	175 (97.8%)	83 (91.2%)	258 (95.6%)	87 (93.5%)	627 (94.4%)
≥ 65 years	15 (7.4%)	4 (4.0%)	19 (6.3%)	4 (2.2%)	8 (8.8%)	12 (4.4%)	6 (6.5%)	37 (5.6%)
Sex at Birth								
Male	95 (47.0%)	48 (48.5%)	143 (47.5%)	101 (56.4%)	49 (53.8%)	150 (55.6%)	49 (52.7%)	342 (51.5%)
Female	107 (53.0%)	51 (51.5%)	158 (52.5%)	78 (43.6%)	42 (46.2%)	120 (44.4%)	44 (47.3%)	322 (48.5%)
Race								
American Indian or Alaska Native	0	0	0	0	0	0	0	0
Asian	56 (27.7%)	29 (29.3%)	85 (28.2%)	41 (22.9%)	19 (20.9%)	60 (22.2%)	28 (30.1%)	173 (26.1%)
Black or African American	4 (2.0%)	0	4 (1.3%)	4 (2.2%)	0	4 (1.5%)	0	8 (1.2%)
Native Hawaiian or Pacific Islander	0	0	0	0	0	0	0	0
White	138 (68.3%)	68 (68.7%)	206 (68.4%)	130 (72.6%)	71 (78.0%)	201 (74.4%)	63 (67.7%)	470 (70.8%)
Other	0	0	0	1 (0.6%)	0	1 (0.4%)	1 (1.1%)	2 (0.3%)
Not Permitted	4 (2.0%)	2 (2.0%)	6 (2.0%)	3 (1.7%)	1 (1.1%)	4 (1.5%)	1 (1.1%)	11 (1.7%)

Ethnicity								
Not Hispanic or Latino	198 (98.0%)	95 (96.0%)	293 (97.3%)	171 (95.5%)	90 (98.9%)	261 (96.7%)	93 (100.0%)	647 (97.4%)
Hispanic or Latino	4 (2.0%)	4 (4.0%)	8 (2.7%)	8 (4.5%)	1 (1.1%)	9 (3.3%)	0	17 (2.6%)
Not Permitted	0	0	0	0	0	0	0	0
Geographic Region								
United States [US]	19 (9.4%)	12 (12.1%)	31 (10.3%)	29 (16.2%)	12 (13.2%)	41 (15.2%)	8 (8.6%)	80 (12.0%)
Non-US	183 (90.6%)	87 (87.9%)	270 (89.7%)	150 (83.8%)	79 (86.8%)	229 (84.8%)	85 (91.4%)	584 (88.0%)
Weight (kg)								
N	202	99	301	179	91	270	93	664
Mean (SD)	71.2 (18.31)	73.0 (18.12)	71.8 (18.24)	72.3 (19.97)	73.7 (18.06)	72.8 (19.32)	69.2 (16.03)	71.8 (18.41)
Median	69.0	72.0	69.5	69.0	71.6	70.0	66.0	69.1
Q1, Q3	58.0, 82.0	58.2, 85.2	58.2, 83.3	58.1, 84.0	60.0, 85.8	59.0, 85.2	57.2, 80.9	58.2, 83.9
Min, Max	38.0, 131.1	41.0, 122.4	38.0, 131.1	39.1, 156.1	41.6, 139.2	39.1, 156.1	40.5, 128.0	38.0, 156.1
Height (cm)								
N	202	99	301	179	90	269	93	663
Mean (SD)	169.2 (9.95)	168.1 (8.98)	168.9 (9.64)	169.8 (9.93)	170.5 (8.70)	170.1 (9.52)	169.1 (9.50)	169.4 (9.58)
Median	169.0	167.0	168.2	170.0	171.1	170.0	168.0	169.8
Q1, Q3	163.0, 176.0	162.8, 173.9	163.0, 175.0	164.0, 176.0	165.0, 177.0	164.0, 176.5	162.5, 175.0	163.0, 176.0
Min, Max	143.8, 197.0	149.0, 187.0	143.8, 197.0	140.0, 198.0	151.6, 195.0	140.0, 198.0	149.0, 190.0	140.0, 198.0

	Induction Filgotinib 200 mg			**Induction Filgotinib 100 mg**			**Induction Placebo**	
	Maintenance Filgotinib 200 mg (N=202)	**Maintenance Placebo (N=99)**	**Total (N=301)**	**Maintenance Filgotinib 100 mg (N=179)**	**Maintenance Placebo (N=91)**	**Total (N=270)**	**Maintenance Placebo (N=93)**	**Overall Total (N=664)**
Body Mass Index (kg/m^2)								
N	202	99	301	179	90	269	93	663
Mean (SD)	24.8 (5.66)	25.7 (5.54)	25.1 (5.63)	24.9 (5.39)	25.2 (5.51)	25.0 (5.42)	24.0 (4.17)	24.9 (5.37)
Median	23.7	25.3	24.2	24.1	23.8	24.0	23.6	24.0
Q1, Q3	20.7, 28.1	21.7, 28.5	21.3, 28.3	20.7, 28.0	21.5, 27.8	21.0, 28.0	20.6, 26.4	21.0, 28.0
Min, Max	14.8, 45.9	16.0, 47.8	14.8, 47.8	15.1, 44.2	17.3, 46.2	15.1, 46.2	17.2, 35.5	14.8, 47.8
Smoking Status								
Former	53 (26.2%)	26 (26.3%)	79 (26.2%)	42 (23.5%)	22 (24.2%)	64 (23.7%)	15 (16.1%)	158 (23.8%)
Current	13 (6.4%)	1 (1.0%)	14 (4.7%)	10 (5.6%)	3 (3.3%)	13 (4.8%)	2 (2.2%)	29 (4.4%)
Never	136 (67.3%)	72 (72.7%)	208 (69.1%)	127 (70.9%)	66 (72.5%)	193 (71.5%)	76 (81.7%)	477 (71.8%)

Max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; US = United States
Percentages were calculated based on the number of subjects in the Safety Analysis Set. Age (in years) was calculated from date of first study drug dosing in the induction studies. Not Permitted = local regulators did not allow collection of race or ethnicity information. Body Mass Index (kg/m^2) = [Weight (kg) / Height (cm)^2] × 10,000. Body Mass Index was calculated based on weight collected on the day of first study drug dosing in the Maintenance Study. Smoking status was based on data collected at screening in the induction studies.

Table 32 GS-US-418-3898: Baseline Disease Characteristics, Maintenance Study (Safety Analysis Set)

	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg			Induction Placebo	Overall Total (N=664)
	Maintenance Filgotinib 200 mg (N=202)	Maintenance Placebo (N=99)	Total (N=301)	Maintenance Filgotinib 100 mg (N=179)	Maintenance Placebo (N=91)	Total (N=270)	Maintenance Placebo (N=93)	
Duration of Ulcerative Colitis (UC, years)								
N	202	99	301	178	91	269	93	663
Mean (SD)	8.4 (7.37)	8.9 (7.61)	8.6 (7.44)	8.9 (8.40)	7.5 (7.45)	8.4 (8.10)	7.0 (6.78)	8.3 (7.64)
Median	6.2	6.7	6.2	6.8	4.9	5.9	5.5	5.8
Q1, Q3	2.5, 12.9	3.1, 13.0	2.7, 12.9	2.6, 12.7	2.4, 9.5	2.4, 12.2	2.0, 9.6	2.5, 12.0
Min, Max	0.5, 36.7	1.0, 29.3	0.5, 36.7	0.5, 48.9	0.6, 39.3	0.5, 48.9	0.6, 38.4	0.5, 48.9
Fecal Calprotectin (µg/g) at Maintenance Baseline								
N	202	99	301	179	91	270	92	663
Mean (SD)	627 (944.9)	934 (2621.7)	728 (1692.4)	662 (1291.2)	760 (1474.7)	695 (1353.9)	1043 (1545.9)	758 (1544.3)
Median	206	167	198	217	277	219	437	222
Q1, Q3	68, 828	73, 537	68, 733	74, 598	52, 923	72, 721	96, 1310	72, 810
Min, Max	29, 5209	29, 22465	29, 22465	29, 10701	29, 11832	29, 11832	29, 7913	29, 22465
C-Reactive Protein (hs-CRP, mg/L) at Maintenance Baseline								
N	202	99	301	179	91	270	93	664
Mean (SD)	3.74 (10.131)	2.72 (4.443)	3.41 (8.686)	3.04 (5.721)	3.53 (5.392)	3.21 (5.607)	3.30 (5.299)	3.31 (7.127)
Median	1.04	1.10	1.05	0.98	1.40	1.12	1.34	1.12
Q1, Q3	0.36, 3.66	0.36, 3.07	0.36, 3.51	0.42, 2.50	0.39, 4.31	0.42, 3.32	0.59, 3.17	0.39, 3.41
Min, Max	0.19, 127.00	0.19, 27.80	0.19, 127.00	0.19, 40.80	0.19, 28.60	0.19, 40.80	0.19, 33.20	0.19, 127.00
Participation in Cohort A or Cohort B								
Cohort A	109 (54.0%)	54 (54.5%)	163 (54.2%)	107 (59.8%)	54 (59.3%)	161 (59.6%)	67 (72.0%)	391 (58.9%)
Cohort B	93 (46.0%)	45 (45.5%)	138 (45.8%)	72 (40.2%)	37 (40.7%)	109 (40.4%)	26 (28.0%)	273 (41.1%)

Treatment History Prior to Induction Baseline								
Number of Prior Biologic Agents Used								
0	110 (54.5%)	55 (55.6%)	165 (54.8%)	106 (59.2%)	56 (61.5%)	162 (60.0%)	68 (73.1%)	395 (59.5%)
1	36 (17.8%)	16 (16.2%)	52 (17.3%)	32 (17.9%)	9 (9.9%)	41 (15.2%)	12 (12.9%)	105 (15.8%)
2	31 (15.3%)	10 (10.1%)	41 (13.6%)	22 (12.3%)	15 (16.5%)	37 (13.7%)	4 (4.3%)	82 (12.3%)
≥ 3	25 (12.4%)	18 (18.2%)	43 (14.3%)	19 (10.6%)	11 (12.1%)	30 (11.1%)	9 (9.7%)	82 (12.3%)
Prior Use of TNF-alpha Antagonist								
Yes	84 (41.6%)	43 (43.4%)	127 (42.2%)	68 (38.0%)	32 (35.2%)	100 (37.0%)	21 (22.6%)	248 (37.3%)
Number of Prior TNF-alpha Antagonists Used								
1	47 (23.3%)	21 (21.2%)	68 (22.6%)	37 (20.7%)	9 (9.9%)	46 (17.0%)	10 (10.8%)	124 (18.7%)
2	29 (14.4%)	19 (19.2%)	48 (15.9%)	26 (14.5%)	21 (23.1%)	47 (17.4%)	9 (9.7%)	104 (15.7%)
≥3	8 (4.0%)	3 (3.0%)	11 (3.7%)	5 (2.8%)	2 (2.2%)	7 (2.6%)	2 (2.2%)	20 (3.0%)
Worst Outcome of Prior TNF-alpha Antagonist Use								
Treatment Failure	76 (37.6%)	39 (39.4%)	115 (38.2%)	62 (34.6%)	29 (31.9%)	91 (33.7%)	18 (19.4%)	224 (33.7%)
Intolerance (allergic and non-allergic)	8 (4.0%)	3 (3.0%)	11 (3.7%)	4 (2.2%)	3 (3.3%)	7 (2.6%)	3 (3.2%)	21 (3.2%)
Other	0	1 (1.0%)	1 (0.3%)	2 (1.1%)	0	2 (0.7%)	0	3 (0.5%)
Prior Use of Vedolizumab								
Yes	49 (24.3%)	24 (24.2%)	73 (24.3%)	32 (17.9%)	16 (17.6%)	48 (17.8%)	15 (16.1%)	136 (20.5%)
Worst Outcome of Prior Vedolizumab Use								
Treatment Failure	40 (19.8%)	21 (21.2%)	61 (20.3%)	28 (15.6%)	14 (15.4%)	42 (15.6%)	12 (12.9%)	115 (17.3%)
Intolerance (allergic and non- allergic)	5 (2.5%)	3 (3.0%)	8 (2.7%)	3 (1.7%)	1 (1.1%)	4 (1.5%)	2 (2.2%)	14 (2.1%)
Other	4 (2.0%)	0	4 (1.3%)	1 (0.6%)	1 (1.1%)	2 (0.7%)	1 (1.1%)	7 (1.1%)

	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg			Induction Placebo	
	Maintenance Filgotinib 200 mg (N=202)	Maintenance Placebo (N=99)	Total (N=301)	Maintenance Filgotinib 100 mg (N=179)	Maintenance Placebo (N=91)	Total (N=270)	Maintenance Placebo (N=93)	Overall Total (N=664)
Prior Use of both TNF-alpha Antagonist and Vedolizumab								
Yes	41 (20.3%)	23 (23.2%)	64 (21.3%)	27 (15.1%)	13 (14.3%)	40 (14.8%)	11 (11.8%)	115 (17.3%)
Concomitant Use of Systemically Absorbed Corticosteroids and Immunomodulator At Maintenance Baseline								
Systemic Corticosteroids Only	61 (30.2%)	31 (31.3%)	92 (30.6%)	62 (34.6%)	28 (30.8%)	90 (33.3%)	25 (26.9%)	207 (31.2%)
Immunomodulators Only	35 (17.3%)	18 (18.2%)	53 (17.6%)	27 (15.1%)	15 (16.5%)	42 (15.6%)	23 (24.7%)	118 (17.8%)
Both Systemic Corticosteroids and Immunomodulators	19 (9.4%)	9 (9.1%)	28 (9.3%)	17 (9.5%)	9 (9.9%)	26 (9.6%)	7 (7.5%)	61 (9.2%)
Neither Systemic Corticosteroids nor Immunomodulators	87 (43.1%)	41 (41.4%)	128 (42.5%)	73 (40.8%)	39 (42.9%)	112 (41.5%)	38 (40.9%)	278 (41.9%)
Systemically Absorbed Corticosteroids								
Yes	80 (39.6%)	40 (40.4%)	120 (39.9%)	79 (44.1%)	37 (40.7%)	116 (43.0%)	32 (34.4%)	268 (40.4%)
Prednisone Equivalence Dose in mg/day								
N	80	40	120	79	37	116	32	268
Mean (SD)	17.0 (8.44)	19.9 (9.43)	17.9 (8.85)	18.1 (8.70)	16.3 (6.43)	17.5 (8.06)	22.0 (8.05)	18.2 (8.50)
Median	20.0	20.0	20.0	20.0	20.0	20.0	22.5	20.0
Q1, Q3	10.0, 20.0	10.0, 30.0	10.0, 25.0	10.0, 25.0	10.0, 20.0	10.0, 20.0	20.0, 30.0	10.0, 25.0
Min, Max	2.5, 40.0	1.0, 30.0	1.0, 40.0	2.5, 30.0	5.0, 30.0	2.5, 30.0	5.0, 30.0	1.0, 40.0
Prednisone Equivalence Dose Group								
> 0 and ≤ 10 mg/day	28 (13.9%)	12 (12.1%)	40 (13.3%)	29 (16.2%)	10 (11.0%)	39 (14.4%)	6 (6.5%)	85 (12.8%)
> 10 and ≤ 20 mg/day	35 (17.3%)	10 (10.1%)	45 (15.0%)	27 (15.1%)	24 (26.4%)	51 (18.9%)	10 (10.8%)	106 (16.0%)
> 20 mg/day	17 (8.4%)	18 (18.2%)	35 (11.6%)	23 (12.8%)	3 (3.3%)	26 (9.6%)	16 (17.2%)	77 (11.6%)
No	122 (60.4%)	59 (59.6%)	181 (60.1%)	100 (55.9%)	54 (59.3%)	154 (57.0%)	61 (65.6%)	396 (59.6%)

Max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; TNF = tumor necrosis factor; UC = ulcerative colitis
Percentages were calculated based on the number of subjects in the Safety Analysis Set. Number of prior use of biologic agents was based on biologics approved for ulcerative colitis only. For use of systemic corticosteroids, only records with routes of oral, intravenous, and intramuscular were included. Duration of UC refers to duration up to induction baseline. History of pancolitis summarizes pancolitis diagnosed prior to induction baseline only.

Numbers analysed

Induction cohort A

Overall, 659 of 660 subjects (99.8%) who were randomised received at least one dose of study drug and were included in both the Safety Analysis Set and the FAS (table below).

Table 33 Cohort A Induction Study

	Filgotinib 200 mg (N=245)	Filgotinib 100 mg (N=278)	Placebo (N=137)	Total (N=660)
All Randomized Analysis Set	245 (100.0%)	278 (100.0%)	137 (100.0%)	660 (100.0%)
Safety Analysis Set	245 (100.0%)	277 (99.6%)	137 (100.0%)	659 (99.8%)
Full Analysis Set	245 (100.0%)	277 (99.6%)	137 (100.0%)	659 (99.8%)
Per-Protocol Analysis Set	235 (95.9%)	253 (91.0%)	125 (91.2%)	613 (92.9%)
Biomarker Analysis Set	244 (99.6%)	271 (97.5%)	137 (100.0%)	652 (98.8%)
PK Analysis Set	242 (98.8%)	263 (94.6%)	0	505 (76.5%)
PK Substudy Analysis Set	4 (1.6%)	11 (4.0%)	0	15 (2.3%)

PK = pharmacokinetic

Induction cohort B

Overall, 689 of 691 randomised subjects (99.7%) received at least one dose of study drug in the Cohort B Induction Study and were included in both the Safety Analysis Set and the FAS (Table below).

Table 34 Cohort B Induction Study

	Filgotinib 200 mg (N=262)	Filgotinib 100 mg (N=286)	Placebo (N=143)	Total (N=691)
All Randomized Analysis Set	262 (100.0%)	286 (100.0%)	143 (100.0%)	691 (100.0%)
Safety Analysis Set	262 (100.0%)	285 (99.7%)	142 (99.3%)	689 (99.7%)
Full Analysis Set	262 (100.0%)	285 (99.7%)	142 (99.3%)	689 (99.7%)
Per-Protocol Analysis Set	235 (89.7%)	251 (87.8%)	123 (86.0%)	609 (88.1%)
Biomarker Analysis Set	262 (100.0%)	285 (99.7%)	142 (99.3%)	689 (99.7%)
PK Analysis Set	249 (95.0%)	271 (94.8%)	0	520 (75.3%)
PK Substudy Analysis Set	9 (3.4%)	17 (5.9%)	0	26 (3.8%)

PK = pharmacokinetic

Maintenance study

Subjects who received placebo in the induction studies and continued placebo in the Maintenance Study, and subjects who did not achieve MCS response or EBS remission in the induction studies were not included in the FAS for the Maintenance Study. A total of 571 subjects who received filgotinib in the induction studies were re-randomized into the Maintenance Study and of these, 558 subjects (97.7%) were included in the FAS.

Table 35 Maintenance Study

	Induction Filgotinib 200 mg		Induction Filgotinib 100 mg		Induction Placebo	
	Maintenance Filgotinib 200 mg (N=202)	Maintenance Placebo (N=99)	Maintenance Filgotinib 100 mg (N=179)	Maintenance Placebo (N=91)	Maintenance Placebo (N=93)	Overall Total (N=664)
All Randomized Analysis Set	202 (100.0%)	99 (100.0%)	179 (100.0%)	91 (100.0%)	93 (100.0%)	664 (100.0%)
Safety Analysis Set	202 (100.0%)	99 (100.0%)	179 (100.0%)	91 (100.0%)	93 (100.0%)	664 (100.0%)
PK Analysis Set	173 (85.6%)	0	136 (76.0%)	0	0	309 (46.5%)
Full Analysis Set	199 (98.5%)	98 (99.0%)	172 (96.1%)	89 (97.8%)	—	558 (97.7%)
Per-Protocol Analysis Set	179 (88.6%)	87 (87.9%)	151 (84.4%)	75 (82.4%)	—	492 (86.2%)
Biomarker Analysis Set	199 (98.5%)	97 (98.0%)	170 (95.0%)	87 (95.6%)	—	553 (96.8%)

PK = pharmacokinetic

Outcomes and estimation

Induction phase:

Cohort A Induction Study–Biologic-Naive Subjects (GS-US-418-3898)

Based on the prespecified hypothesis testing order statistically significant treatment differences between filgotinib 200 mg and placebo at Week 10 were observed for the primary and all key

secondary endpoints. Treatment differences between filgotinib 100 mg and placebo were not statistically significant for the primary and key secondary endpoints at Week 10.

Primary endpoint

Table 36 GS-US-418-3898: Proportion of Subjects with EBS Remission at Week 10, Cohort A Induction Study (Non-responder Imputation; Full Analysis Set

	Filgotinib 200 mg (N=245)	Filgotinib 100 mg (N=277)	Placebo (N=137)
Number (%) of Subjects Achieving EBS Remission at Week 10	64 (26.1%)	53 (19.1%)	21 (15.3%)
95% CI for the Proportion	20.4% to 31.8%	14.3% to 23.9%	8.9% to 21.7%
Comparison with Placebo			
Non-Stratified Risk Difference in Proportions and 95% CI	10.8% (2.1% to 19.5%)	3.8% (−4.3% to 12.0%)	
p-value from Stratified CMH Test	0.0157	0.3379	
Stool Frequency Subscore of 0	43 (67.2%)	40 (75.5%)	15 (71.4%)
Stool Frequency Subscore of 1	21 (32.8%)	13 (24.5%)	6 (28.6%)
Number (%) of Subjects Not Achieving EBS Remission at Week 10	181 (73.9%)	224 (80.9%)	116 (84.7%)
Observed Non-responders	171 (69.8%)	206 (74.4%)	104 (75.9%)
Non-responders due to Treatment Failure	1 (0.4%)	2 (0.7%)	3 (2.2%)
Early Termination	7 (2.9%)	14 (5.1%)	8 (5.8%)
Insufficient Data due to Other Reasons	2 (0.8%)	2 (0.7%)	1 (0.7%)

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EBS = endoscopy/bleeding/stool frequency; UC = ulcerative colitis
EBS remission was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1 point decrease in stool frequency subscore from induction baseline to achieve 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction. The CMH test was stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. The denominator of percentage for stool frequency subscore of 0 or 1 was the number of subjects achieving EBS remission at Week 10.

Sensitivity analyses:

When locally read endoscopic subscore was used to assess EBS remission instead of the centrally read sub score, the treatment effect of filgotinib compared with placebo was greater for both filgotinib 200 mg and filgotinib 100mg:

- Filgotinib 200 mg: 34.7%, placebo: 19.7%; difference in proportions: 15.0%, 95% CI: 5.5% to 24.5%, p = 0.0023
- Filgotinib 100 mg: 26.4%, placebo: 19.7%; difference in proportions: 6.6%, 95% CI: −2.3% to 15.6%, p = 0.1407

The number of subjects with missing primary efficacy data, which was not due to early termination or treatment failure, was small and balanced across treatment groups; however, a higher proportion of subjects in the placebo group had missing primary efficacy data due to early termination compared with the filgotinib groups (filgotinib 200 mg: 2.9%; filgotinib 100mg: 5.1%; placebo: 5.8%). As the MAH states this limits the interpretation of the results of sensitivity analyses using different approaches to impute missing data. The estimated treatment differences between filgotinib and placebo for EBS remission using observed cases only or the multiple imputation method were consistent with the primary analysis results for both filgotinib 200 mg and filgotinib 100 mg. When using missing = success, or missing = success for placebo and missing = failure for filgotinib, the treatment effect of filgotinib compared with placebo was smaller for both filgotinib 200 mg and filgotinib 100 mg.

Key secondary endpoints

Table 37 GS-US-418-3898: Cohort A Induction Study—Hierarchical Testing of the Superiority of Filgotinib versus Placebo at Week 10 (Non-responder Imputation; Full Analysis Set)

Endpoint	Filgotinib vs Placebo (n/N) Difference (95% CI)	P-Value
Filgotinib 200 mg vs Placebo		
EBS Remission (%)[a]	26.1% (64/245) vs 15.3% (21/137) 10.8% (2.1%, 19.5%)	0.0157[b]
MCS Remission (%)	24.5% (60/245) vs 12.4% (17/137) 12.1% (3.8%, 20.4%)	0.0053[b]
Endoscopic Subscore of 0 (%)	12.2% (30/245) vs 3.6% (5/137) 8.6% (2.9%, 14.3%)	0.0047[b]
Geboes Histologic Remission (%)	35.1% (86/245) vs 16.1% (22/137) 19.0% (9.9%, 28.2%)	< 0.0001[b]
MCS Remission (Alternative Definition) (%)	12.2% (30/245) vs 4.4% (6/137) 7.9% (1.9%, 13.8%)	0.0105[b]
Filgotinib 100 mg vs Placebo		
EBS Remission (%)[a]	19.1% (53/277) vs 15.3% (21/137) 3.8% (−4.3%, 12.0%)	0.3379
MCS Remission (%)	17.0% (47/277) vs 12.4% (17/137) 4.6% (−3.1%, 12.2%)	0.2295
Endoscopic Subscore of 0 (%)	5.8% (16/277) vs 3.6% (5/137) 2.1% (−2.6%, 6.8%)	0.3495
Geboes Histologic Remission (%)	23.8% (66/277) vs 16.1% (22/137) 7.8% (−0.7%, 16.2%)	0.0672
MCS Remission (Alternative Definition) (%)	8.7% (24/277) vs 4.4% (6/137) 4.3% (−1.0%, 9.6%)	0.1062

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EBS = endoscopy/bleeding/stool frequency; MCS = Mayo Clinic Score
a Primary endpoint
b Statistically significant P-value
The 95% CIs are calculated based on normal approximation with a continuity correction. P-values are based on CMH test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1.

Exploratory outcomes

Table 38 GS-US-418-3898: Cohort A Induction Study—Summary of Selected Dichotomous Exploratory Endpoints, Comparisons of Filgotinib versus Placebo at Week 10 (Non-responder imputation; Full Analysis Set)

Endpoint	Filgotinib vs Placebo (n/N) Difference (95% CI)	Nominal P-Value
Filgotinib 200 mg vs Placebo		
Endoscopic Response (%)	33.9% (83/245) vs 20.4% (28/137) 13.4% (3.9%, 23.0%)	0.0055
MCS Response (%)	66.5% (163/245) vs 46.7% (64/137) 19.8% (9.0%, 30.6%)	0.0002
EBS Remission (Alternative Definition) (%)	27.8% (68/245) vs 15.3% (21/137) 12.4% (3.6%, 21.2%)	0.0063
Filgotinib 100 mg vs Placebo		
Endoscopic Response (%)	26.4% (73/277) vs 20.4% (28/137) 5.9% (3.1%, 15.0%)	0.1760
MCS Response (%)	59.2% (164/277) vs 46.7% (64/137) 12.5% (1.8%, 23.2%)	0.0173
EBS Remission (Alternative Definition) (%)	20.9% (58/277) vs 15.3% (21/137) 5.6% (2.6%, 13.9%)	0.1694

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EBS = endoscopy/bleeding/stool frequency; MCS = Mayo Clinic Score

Endoscopic response was defined as having endoscopic subscore of 0 or 1. MCS response was defined as having an MCS reduction of ≥ 3 points and at least 30% from induction baseline score with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1. EBS remission (alternative definition) was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and stool frequency subscore of 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction. CMH test was stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1.

Change from Baseline in Partial MCS (LoCF)

Week 2:

Filgotinib 200mg: −1 .8 (1.81), placebo: −1.2 (1.61); Least-square mean (LSM) difference (SE): −0.6 (0.18), p = 0.0005.
Filgotinib 100 mg: −1 .4 (1.79), placebo: −1.2 (1.61); LSM difference (SE): −0. 4 (0.18), p = 0.0433

Week 4:

Filgotinib 200mg: −2.4 (2.11), placebo: −1.7 (1.97); LSM difference (SE): −0.8 (0.21), p < 0.0001.
Filgotinib 100 mg: −2.1 (2.04), placebo: −1.7 (1.97); LSM difference (SE): −0.5 (0.20), p = 0.0088

Week 6:

Filgotinib 200mg: −3.0 (2.21), placebo: −1.9 (2.09); LSM difference (SE): −1.2 (0.22), p < 0.0001
Filgotinib 100 mg: −2. 6 (2. 19), placebo: −1.9 (2.09); LSM difference (SE): −0. 8 (0.21), p = 0.0003

Week 10

Filgotinib 200mg: −3.4 (2.23), placebo: −2.2 (2.41); LSM difference (SE): −1.3 (0.23), p < 0.0001
Filgotinib 100 mg: −2.8 (2.31), placebo: −2.2 (2.41); LSM difference (SE): −0.7 (0.22), p = 0.001.

SF-36

Physical Component Summary

Filgotinib 200mg: 6.78 (6.850), placebo: 3.10 (7.309); LSM difference (SE):3.52 (0.678), p < 0.0001

Filgotinib 100 mg: 5.69 (7.430), placebo: 3.10 (7.309); LSM difference (SE):2.34 (0.664), p = 0.0005

Mental Component Summary

Filgotinib 200mg: 8.04 (10.178), placebo: 6.12 (9.319); LSM difference (SE):3.02 (0.933), p= 0.0013

Filgotinib 100 mg: 6.81 (10.613), placebo: 6.12 (9.319); LSM difference (SE):1.66 (0.914), p= 0.06

EQ-5D

Mobility: filgotinib 200mg: 27.1%; filgotinib 100mg: 23.8%; placebo: 21.8%

Self-care: filgotinib 200mg: 6.6%; filgotinib 100mg: 9.5%; placebo: 7.3%

Usual activities: filgotinib 200mg: 50.2%; filgotinib 100mg: 53.6%; placebo: 41.1%

Pain/discomfort: filgotinib 200mg: 54.6%; filgotinib 100mg: 56.0%; placebo: 42.7%

Anxiety/depression: filgotinib 200mg: 49.3%; filgotinib 100mg: 44.4%; placebo: 36.3%

EQ-VAS

Filgotinib 200mg: 17 (21.5) mm, placebo: 9 (21.3) mm; LSM difference (SE): 9 (1.8) mm, p < 0.0001

Filgotinib 100mg: 16 (21.4) mm, placebo: 9 (21.3) mm; LSM difference (SE): 8 (1.8) mm, p < 0.0001

IBDQ

Bowel Symptoms

Filgotinib 200mg: 1.8 (1.19), placebo: 1.2 (1.31); LSM difference (SE):0.7 (0.12), p < 0.0001

Filgotinib 100mg: 1.7 (1.30), placebo: 1.2 (1.31); LSM difference (SE):0.5 (0.12), p < 0.0001

Systemic Symptoms

Filgotinib 200mg: 1.6 (1.28), placebo: 1.0 (1.49); LSM difference (SE):0.7 (0.12), p < 0.0001

Filgotinib 100mg: 1.5 (1. 32), placebo: 1.0 (1.49); LSM difference (SE):0.5 (0.12), p < 0.0001

Emotional Function

Filgotinib 200mg: 1.5 (1.25), placebo: 0.9 (1.23); LSM difference (SE):0.6 (0.12), p < 0.0001

Filgotinib 100mg: 1.3 (1.35), placebo: 0.9 (1.23); LSM difference (SE):0.4 (0.12), p = 0.0002

Social Function

Filgotinib 200mg: 1.7 (1.60), placebo: 1.2 (1.54); LSM difference (SE):0.6 (0 .14), p < 0.0001

Filgotinib 100mg: 1.6 (1.51), placebo: 1.2 (1.54); LSM difference (SE):0.5 (0.14), p = 0.0004

IBDQ Total Scores

Filgotinib 200mg: 52 (37.8), placebo: 34 (40.5); LSM difference (SE): 21 (3.7), p < 0.0001

Filgotinib 100 mg: 49 (40.2), placebo: 34 (40.5); LSM difference (SE): 15 (3.6), p < 0.000

WPAI

Absenteeism

Filgotinib 200mg: −10.0 (30.65), placebo: −10.0 (33.76); LSM difference (SE): −4.0(2.99), p = 0.1817

Filgotinib 100 mg: −5.9 (25.96), placebo: −10.0 (33.76); LSM difference (SE):0.1 (2.88), p = 0.9713

Presenteeism

Filgotinib 200mg: −21.8 (26.49), placebo: −9.5 (25.63); LSM difference (SE): −14.5(3.19), p < 0.0001

Filgotinib 100 mg: −18.4 (25.58), placebo: −9.5 (25.63); LSM difference (SE): −10.1 (3.05), p = 0.0011

Work Productivity Loss

Filgotinib 200mg: −24 .5 (33.48), placebo: −16.4 (32.92); LSM difference (SE): −12.4 (3.79), p = 0.0011

Filgotinib 100 mg: −21 .5 (32.15), placebo: −16.4 (32.92); LSM difference (SE): −8.7 (3.65), p= 0.0173

Activity Impairment

Filgotinib 200mg: −24.0 (28.18), placebo: −12.0 (27.23); LSM difference (SE): −13.1 (2.58), p< 0.0001

Filgotinib 100 mg: −20 .8 (30.68), placebo: −12.0 (27.23); LSM difference (SE): −8 .8 (2.52), p = 0.0005

Change from Baseline in Biomarkers

Biomarker assessments included change from baseline in systemic or localized inflammatory biomarkers, including hs-CRP and faecal calprotectin. Overall, 652 subjects from the Cohort A Induction Study were included in the Biomarker Analysis Set. Decreases from baseline in hs-CRP values were observed at 2 weeks after starting treatment with filgotinib in both the filgotinib 200 mg and filgotinib 100 mg groups. From baseline to Week 10, greater decreases in faecal calprotectin were observed in both the filgotinib 200 mg and filgotinib 100 mg groups compared with the placebo group.

Cohort B Induction Study–Biologic-experienced Subjects (GS-US-418-3898)

Primary endpoint

Table 39 S-US-418-3898: Proportion of Subjects with EBS Remission at Week 10, Cohort B Induction Study (Nonresponder Imputation; Full Analysis Set

	Filgotinib 200 mg (N=262)	Filgotinib 100 mg (N=285)	Placebo (N=142)
Number (%) of Subjects Achieving EBS Remission at Week 10	30 (11.5%)	27 (9.5%)	6 (4.2%)
95% CI for the Proportion	7.4% to 15.5%	5.9% to 13.0%	0.6% to 7.9%
Comparison with Placebo			
Non-Stratified Risk Difference in Proportions and 95% CI	7.2% (1.6% to 12.8%)	5.2% (-0.0% to 10.5%)	
p-value from Stratified CMH Test	0.0103	0.0645	
Stool Frequency Subscore of 0	17 (56.7%)	17 (63.0%)	4 (66.7%)
Stool Frequency Subscore of 1	13 (43.3%)	10 (37.0%)	2 (33.3%)
Number (%) of Subjects Not Achieving EBS Remission at Week 10	232 (88.5%)	258 (90.5%)	136 (95.8%)
Observed Non-responders	206 (78.6%)	227 (79.6%)	119 (83.8%)
Non-responders due to Treatment Failure	3 (1.1%)	4 (1.4%)	4 (2.8%)
Early Termination	18 (6.9%)	21 (7.4%)	11 (7.7%)
Insufficient Data due to Other Reasons	5 (1.9%)	6 (2.1%)	2 (1.4%)

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EBS = endoscopy/bleeding/stool frequency; UC = ulcerative colitis
EBS remission was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1 point decrease in stool frequency subscore from Induction baseline to achieve 0 or 1. The 95% CIs are calculated based on normal approximation with a continuity correction. The CMH test was stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1, and number of prior exposure to biologic agents (≤1, >1).
Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. The denominator of the percentage for stool frequency subscore of 0 or 1 was the number of subjects achieving EBS remission at Week 10.

Sensitivity analysis primary endpoint

Sensitivity analyses of the primary endpoint were performed and included analyses based on the PP Analysis Set, locally read endoscopic subscore instead of centrally read subscore, and different missing data imputation rules (ie, observed cases only, missing= success, missing= success for placebo and missing= failure for filgotinib, and multiple imputation).

When locally read endoscopic subscore was used to assess EBS remission instead of the centrally read subscore, the treatment effect of filgotinib compared with placebo was greater for both filgotinib 200 mg and filgotinib 100mg.

- Filgotinib 200 mg: 22.9%, placebo: 4.9%; difference in proportions: 18.0%, 95% CI: 11.2% to 24.7%, $p < 0.0001$
- Filgotinib 100 mg: 12.6%, placebo: 4.9%; difference in proportions: 7.7%, 95% CI: 1.9% to 13.5%, $p = 0.0127$

In the analysis using multiple imputation the outcome was:

- Filgotinib 200 mg: 12.5%, placebo: 4.8%; difference in proportions: 7.7%, 95% CI: 1.6% to 13.8%, $p = 0.0104$
- Filgotinib 100 mg: 10.5%, placebo: 4.8%; difference in proportions: 5.6%, 95% CI: −0.1% to 11.4%, $p = 0.0651$

Key secondary endpoints

Table 40 GS-US-418-3898: Cohort B Induction Study—Hierarchical Testing of the Superiority of Filgotinib versus Placebo at Week10 (Nonresponder Imputation; Full Analysis Set)

Endpoint	Filgotinib vs Placebo (n/N) Difference (95% CI)	P-Value
Filgotinib 200 mg vs Placebo		
EBS Remission (%)[a]	11.5% (30/262) vs 4.2% (6/142) 7.2% (1.6%, 12.8%)	0.0103[b]
MCS Remission (%)	9.5% (25/262) vs 4.2% (6/142) 5.3% (−0.1%, 10.7%)	0.0393
Endoscopic Subscore of 0 (%)	3.4% (9/262) vs 2.1% (3/142) 1.3% (−2.5%, 5.1%)	0.4269
Geboes Histologic Remission (%)	19.8% (52/262) vs 8.5% (12/142) 11.4% (4.2%, 18.6%)	0.0019
MCS Remission (Alternative Definition) (%)	3.8% (10/262) vs 2.1% (3/142) 1.7% (−2.2%, 5.6%)	0.3084
Filgotinib 100 mg vs Placebo		
EBS Remission (%)[a]	9.5% (27/285) vs 4.2% (6/142) 5.2% (−0.0%, 10.5%)	0.0645
MCS Remission (%)	6.0% (17/285) vs 4.2% (6/142) 1.7% (−3.1%, 6.6%)	0.5308
Endoscopic Subscore of 0 (%)	2.1% (6/285) vs 2.1% (3/142) −0.0% (−3.4%, 3.4%)	0.9987
Geboes Histologic Remission (%)	13.7% (39/285) vs 8.5% (12/142) 5.2% (−1.4%, 11.8%)	0.1286
MCS Remission (Alternative Definition) (%)	2.1% (6/285) vs 2.1% (3/142) −0.0% (−3.4%, 3.4%)	0.9109

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EBS = endoscopy/bleeding/stool frequency; MCS = Mayo Clinic Score

a Primary endpoint

b Statistically significant P-value

The 95% CIs were calculated based on normal approximation with a continuity correction. The CMH test was stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1, and number of prior exposures to biologic agent (≤1, >1).

Exploratory endpoints

Table 41 GS-US-418-3898: Cohort B Induction Study—Summary of Selected Dichotomous Exploratory Endpoints, Comparisons of Filgotinib versus Placebo at Week 10 (Non-responder Imputation; Full Analysis Set)

Endpoint	Filgotinib vs Placebo (n/N) Difference (95% CI)	Nominal P-Value
Filgotinib 200 mg vs Placebo		
Endoscopic Response (%)	17.2% (45/262) vs 7.7% (11/142) 9.4% (2.5%, 16.3%)	0.0053
MCS Response (%)	53.1% (139/262) vs 17.6% (25/142) 35.4% (26.2%, 44.7%)	< 0.0001
EBS Remission (Alternative Definition) (%)	13.0% (34/262) vs 4.9% (7/142) 8.0% (2.1%, 14.0%)	0.0062
Filgotinib 100 mg vs Placebo		
Endoscopic Response (%)	13.0% (37/285) vs 7.7% (11/142) 5.2% (−1.2%, 11.6%)	0.1138
MCS Response (%)	35.8% (102/285) vs 17.6% (25/142) 18.2% (9.3%, 27.1%)	0.0001
EBS Remission (Alternative Definition) (%)	9.5% (27/285) vs 4.9% (7/142) 4.5% (−0.9%, 10.0%)	0.1174

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EBS = endoscopy/bleeding/stool frequency; MCS = Mayo Clinic Score

Endoscopic response was defined as having endoscopic subscore of 0 or 1. MCS response was defined as having an MCS reduction of ≥ 3 points and at least 30% from induction baseline score with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1. EBS remission (alternative definition) was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and stool frequency subscore of 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction. CMH test was stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1, and number of prior exposure to biologic agent (≤ 1, > 1).

Change from Baseline in Partial MCS

Week2 :

Filgotinib 200mg: −1.7 (1.75), placebo: −0.8 (1.45); LSM difference (SE): −0.9 (0.16), p < 0 .0001

Filgotinib 100 mg: −1.2 (1.49), placebo: −0.8 (1.45); LSM difference (SE): −0.4 (0.16), p = 0.0114

Week 4:

Filgotinib 200mg: −2. 2 (2.08), placebo: −1.0 (1.65); LSM difference (SE): −1 .2 (0. 19), p < 0.0001

Filgotinib 100 mg: −1 .6 (1.79), placebo: −1.0 (1.65); LSM difference (SE): −0. 6 (0. 18), p = 0.0015

Week 6:

Filgotinib 200mg: −2 .6 (2.23), placebo: −1.1 (1.87); LSM difference (SE): −1. 4 (0.20), p < 0.0001

Filgotinib 100 mg: −1 .8 (1.92), placebo: −1.1 (1.87); LSM difference (SE): −0. 7 (0.20), p = 0.0003

Week 10:

Filgotinib 200mg: −2 .8 (2. 32), placebo: −1.0 (1.90); LSM difference (SE): −1. 7 (0.22), p < 0.0001

Filgotinib 100 mg: −2. 0 (2. 20), placebo: −1.0 (1.90); LSM difference (SE): −0. 9 (0.22), p < 0.0001

SF-36

SF-36 Physical Component Summary

Filgotinib 200mg: 6.61 (7.278), placebo: 2.44 (8.062); LSM difference (SE):4.02 (0.691), p < 0.0001

Filgotinib 100 mg: 4.16 (6.622), placebo: 2.44 (8.062); LSM difference (SE):2.24 (0.682), p = 0.0011

SF-36 Mental Component Summary

Filgotinib 200mg: 7.92 (10.409), placebo: 1.66 (9.540); LSM difference (SE):4.97 (0.913), p < 0.0001

Filgotinib 100 mg: 3.85 (9.512), placebo: 1.66 (9.540); LSM difference (SE):2.28 (0.896), p = 0.0113

EQ-5D

From baseline to Week10, the percentage of subjects who reported an improvement in the specific health dimensions were as follows:

Mobility: filgotinib 200mg: 27.1%; filgotinib 100 mg: 22.4%; placebo: 22.9%

Self-care: filgotinib 200mg: 8.7%; filgotinib 100mg: 5.9%; placebo: 6.8%

Usual activities: filgotinib 200mg: 49.3%; filgotinib 100mg: 40.9%; placebo: 36.4%

Pain/discomfort: filgotinib 200mg: 58.1%; filgotinib 100mg: 44.1%; placebo: 33.9%

Anxiety/depression: filgotinib 200mg: 41.0%; filgotinib 100mg: 34.3%; placebo: 30.5%

EQ-VAS

Filgotinib 200mg: 19 (22.2) mm, placebo:6 (20.2) mm; LSM difference (SE): 12 (1.9) mm, p < 0.0001

Filgotinib 100mg: 10 (21.2) mm, placebo: 6 (20.2) mm; LSM difference (SE): 5 (1.9) mm, p = 0.0051

WPAI

Pairwise comparisons (mean [SD]) for each filgotinib treatment group versus placebo were as follows:

Absenteeism

Filgotinib 200mg:−12.1 (28.26), placebo:−7.8 (27.72); LSM difference(SE):−2.8 (2.79), p= 0.3259
Filgotinib 100 mg:−6 .6 (24.19), placebo:−7.8 (27.72); LSM difference (SE):−1.7 (2.71), p=0.5297

Presenteeism

Filgotinib 200mg:−18.1 (24.74), placebo:−6.1 (27.81); LSM difference (SE):−9 .3 (3.25), p=0.0042
Filgotinib 100 mg: −12 .1 (2 8.70), placebo: −6.1 (27.81); LSM difference (SE):−4.8 (3.12), p = 0.126

Work Productivity Loss

Filgotinib 200mg:−2 2.0 (32.45), placebo:−10.6 (30.24); LSM difference (SE):−10.6 (3.75), p = 0.0048 Filgotinib 100 mg:−12 .9 (33.38), placebo:−10.6 (30.24); LSM difference (SE):−4.3 (3.65), p = 0.2424

Activity Impairment

Filgotinib 200mg:−24.3 (2 9.06), placebo:−6.4 (29.86); LSM difference (SE):−15.1 (2.68), p < 0.0001 Filgotinib 100 mg: −15 .9 (28.83), placebo: −6.4 (29.86); LSM difference (SE):−8. 5 (2.63), p = 0.0014

Change from Baseline in Biomarkers

Biomarker assessments included change from baseline in systemic or localized inflammatory biomarkers, including hs-CRP and fecal calprotectin. Overall, 689 subjects from the Cohort B Induction Study were included in the Biomarker Analysis Set. Decreases from baseline in hs-CRP values were observed 2 weeks after starting treatment with filgotinib in both the filgotinib 200 mg and filgotinib 100 mg groups. From baseline to Week10, fecal calprotectin decreased in both the filgotinib 200 mg and filgotinib100 mg groups.

Maintenance Study (GS-US-418-3898)

Primary endpoint

Based on the prespecified hypothesis testing order, statistically significant treatment differences between filgotinib 200 mg and placebo at Week 58 were observed for the primary and all key secondary endpoints. Treatment differences between filgotinib 100mg and respective placebo were statistically significant for the primary endpoint, but not for the key secondary endpoints at Week 58. A summary of results for the primary and key secondary endpoints in the Maintenance Study is provided in the tables below.

Disease worsening starting at 11 weeks of therapy was based on the following criteria:

- partial MCS score (all components of MCS except for endoscopic subscore) increase of ≥ 3 points to at least 5 points from the Week 10 value on two consecutive visits, or an increase to 9 points on two consecutive visits if the Week 10 value is >6.
- The disease worsening visits may include unscheduled visits (eg, a study visit followed by an unscheduled visit, or 2 sequential unscheduled visits anytime from Week 11 onward).
- Disease worsening to the extent that the subject clinically requires medications prohibited by the study (at investigator discretion, with discussion with medical monitor if feasible); these subjects do not qualify for the LTE study.

Table 42 GS-US-418-3898: Proportion of Subjects with EBS Remission at Week 58, Maintenance Study (Non-responder Imputation; Full Analysis Set)

	Induction Filgotinib 200 mg		Induction Filgotinib 100 mg	
	Maintenance Filgotinib 200 mg (N=199)	Maintenance Placebo (N=98)	Maintenance Filgotinib 100 mg (N=172)	Maintenance Placebo (N=89)
Number (%) of Subjects Achieving EBS Remission at Week 58	74 (37.2%)	11 (11.2%)	41 (23.8%)	12 (13.5%)
95% CI for the Proportion	30.2% to 44.2%	4.5% to 18.0%	17.2% to 30.5%	5.8% to 21.1%
Comparison with Placebo				
Non-Stratified Risk Difference in Proportions and 95% CI	26.0% (16.0% to 35.9%)		10.4% (-0.0% to 20.7%)	
p-value from Stratified CMH Test	< 0.0001		0.0420	
Stool Frequency Subscore of 0	60 (81.1%)	7 (63.6%)	29 (70.7%)	10 (83.3%)
Stool Frequency Subscore of 1	14 (18.9%)	4 (36.4%)	12 (29.3%)	2 (16.7%)
Number (%) of Subjects Not Achieving EBS Remission at Week 58	125 (62.8%)	87 (88.8%)	131 (76.2%)	77 (86.5%)
Observed Non-responders	73 (36.7%)	28 (28.6%)	57 (33.1%)	26 (29.2%)
Non-responders due to Treatment Failure	1 (0.5%)	2 (2.0%)	3 (1.7%)	1 (1.1%)
Protocol-specified Disease Worsening (PSDW)	34 (17.1%)	48 (49.0%)	52 (30.2%)	39 (43.8%)
Early Termination without PSDW	15 (7.5%)	8 (8.2%)	16 (9.3%)	9 (10.1%)
Insufficient Data due to Other Reasons	2 (1.0%)	1 (1.0%)	3 (1.7%)	2 (2.2%)

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EBS = endoscopy/bleeding/stool frequency; PSDW = protocol-specified disease worsening; UC = ulcerative colitis
EBS remission was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a one point decrease in stool frequency subscore from induction baseline to achieve 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction. The CMH test was stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at maintenance baseline, and participating in the Cohort A Induction Study or the Cohort B Induction Study. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. The denominator of percentage for stool frequency subscore of 0 or 1 was the number of subjects achieving EBS remission at Week 58.

Sensitivity analyses

When locally read endoscopic subscore was used to assess EBS remission instead of the centrally read subscore, the treatment effect of filgotinib compared with placebo was greater for both filgotinib 200 mg and filgotinib 100 mg;

- Filgotinib 200 mg: 51.3%, placebo: 19.4%; difference in proportions: 31.9%, 95% CI: 20.6% to 43.1%, $p < 0.0001$
- Filgotinib 100 mg: 36.6%, placebo: 21.3%; difference in proportions: 15.3%, 95% CI: 3.3% to 27.3%, $p = 0.0076$

Higher proportions of subjects who were re-randomised from filgotinib in the induction studies to placebo in the Maintenance Study prematurely discontinued study drug compared with subjects who continued on filgotinib: 25.7% in the filgotinib 200 mg group compared with 58.6% in the respective placebo group, and 41.9% in the filgotinib 100 mg group compared with 53.8% in the respective placebo group). Even with these different rates of discontinuation across treatment groups, the estimated treatment differences between filgotinib and placebo for EBS remission using different missing value imputation methods were consistent with the primary analysis results for both filgotinib 200 mg and filgotinib 100mg, with the exception of a lower EBS remission rate in the filgotinib 100 mg

group compared with placebo when using the most conservative approach (missing = success for placebo and missing= failure for filgotinib).

Key secondary endpoints

Table 43 GS-US-418-3898: Maintenance Study —Hierarchical Testing of the Superiority of Filgotinib versus Placebo at Week 58 (Non-responder Imputation; Full Analysis Set)

Endpoint	Filgotinib vs Placebo (n/N) Difference (95% CI)	P-Value
Filgotinib 200 mg vs Placebo		
EBS Remission (%)[a]	37.2% (74/199) vs 11.2% (11/98) 26.0% (16.0%, 35.9%)	< 0.0001[b]
6-month Corticosteroid-free EBS Remission (%)[c]	27.2% (25/92) vs 6.4% (3/47) 20.8% (7.7%, 33.9%)	0.0055[b]
Sustained EBS Remission (%)	18.1% (36/199) vs 5.1% (5/98) 13.0% (5.3%, 20.6%)	0.0024[b]
MCS Remission (%)	34.7% (69/199) vs 9.2% (9/98) 25.5% (16.0%, 35.0%)	< 0.0001[b]
Endoscopic Subscore of 0 (%)	15.6% (31/199) vs 6.1% (6/98) 9.5% (1.8%, 17.1%)	0.0157[b]
Geboes Histologic Remission (%)	38.2% (76/199) vs 13.3% (13/98) 24.9% (14.6%, 35.2%)	< 0.0001[b]
MCS Remission (Alternative Definition) (%)	22.1% (44/199) vs 6.1% (6/98) 16.0% (7.8%, 24.2%)	0.0005[b]
Filgotinib 100 mg vs Placebo		
EBS Remission (%)[a]	23.8% (41/172) vs 13.5% (12/89) 10.4% (0.0%, 20.7%)	0.0420[b]
6-month Corticosteroid-free EBS Remission (%)[c]	13.6% (11/81) vs 5.4% (2/37) 8.2% (4.2%, 20.6%)	0.1265
Sustained EBS Remission (%)	8.7% (15/172) vs 7.9% (7/89) 0.9% (7.0%, 8.7%)	0.7951
MCS Remission (%)	22.7% (39/172) vs 13.5% (12/89) 9.2% (1.1%, 19.5%)	0.0658
Endoscopic Subscore of 0 (%)	13.4% (23/172) vs 7.9% (7/89) 5.5% (2.9%, 13.9%)	0.1808
Geboes Histologic Remission (%)	27.9% (48/172) vs 18.0% (16/89) 9.9% (1.3%, 21.2%)	0.0521
MCS Remission (Alternative Definition) (%)	12.2% (21/172) vs 7.9% (7/89) 4.3% (3.9%, 12.6%)	0.2946

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EBS = endoscopy/bleeding/stool frequency; MCS = Mayo Clinic Score

a Primary endpoint

b Statistically significant P-value

c Denominator of percentage is the number of Full Analysis Set subjects who were on corticosteroid at maintenance baseline. The 95% CIs were calculated based on normal approximation with a continuity correction. The CMH test was stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at maintenance baseline, and by participation in the Cohort A Induction Study or Cohort B Induction Study.

Exploratory endpoints

Table 44 GS-US-418-3898: Maintenance Study—Summary of Dichotomous Exploratory Efficacy Endpoints, Comparisons of Filgotinib versus Placebo (Non-responder Imputation; Full Analysis Set)

Endpoint	Filgotinib vs Placebo (n/N) Difference (95% CI)	Nominal P-Value
Filgotinib 200 mg vs Placebo		
Sustained MCS Remission	15.1% (30/199) vs 5.1% (5/98) 10.0% (2.6%, 17.3%)	0.0123
6-month Corticosteroid-Free MCS Remission[a]	27.2% (25/92) vs 4.3% (2/47) 22.9% (10.5%, 35.3%)	0.0018
Novel Histologic Outcomes	30.2% (60/199) vs 11.2% (11/98) 18.9% (9.2%, 28.6%)	0.0003
Endoscopic Response	40.7% (81/199) vs 15.3% (15/98) 25.4% (14.8%, 36.0%)	< 0.0001
MCS Response	66.8% (133/199) vs 32.7% (32/98) 34.2% (22.1%, 46.3%)	< 0.0001
EBS Remission (Alternative Definition)	37.2% (74/199) vs 12.2% (12/98) 24.9% (14.8%, 35.0%)	< 0.0001
Filgotinib 100 mg vs Placebo		
Sustained MCS Remission	6.4% (11/172) vs 7.9% (7/89) −1.5% (−9.0%, 6.1%)	0.6501
6-month Corticosteroid-Free MCS Remission[a]	12.3% (10/81) vs 5.4% (2/37) 6.9% (−5.2%, 19.1%)	0.1742
Novel Histologic Outcomes	23.8% (41/172) vs 13.5% (12/89) 10.4% (−0.0%, 20.7%)	0.0404
Endoscopic Response	26.7% (46/172) vs 19.1% (17/89) 7.6% (−3.7%, 19.0%)	0.1625
MCS Response	50.6% (87/172) vs 39.3% (35/89) 11.3% (−2.2%, 24.7%)	0.0703
EBS Remission (Alternative Definition)	24.4% (42/172) vs 13.5% (12/89) 10.9% (0.5%, 21.4%)	0.0331

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EBS = endoscopy/bleeding/stool frequency; MCS = Mayo Clinic Score; SAP = statistical analysis plan; UC = ulcerative colitis

a Denominator of percentage was the number of Full Analysis Set subjects who were on corticosteroids at maintenance baseline.

Six-month corticosteroid-free MCS remission at Week 58 was defined as achieving MCS remission with no corticosteroid use for the indication of UC for at least 6 months prior to Week 58. Novel histologic outcomes were defined by the SAP-specified Geboes Scale, as having Grade 0 of ≤ 0.3, Grade 1 of ≤ 1.1, Grade 2a of 2A.0, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0,

Change from Baseline in MCS – Maintenance Study

Observed values: Mean (SD) changes from maintenance baseline in MCS at Week58 were as follows: filgotinib 200mg: −0 .7 (2.27); respective placebo: 0.7 (2.38); filgotinib 100mg: −0 .4 (2.28); respective placebo: −0.6 (1.80).

Changes from maintenance baseline in MCS at Week58 (LOCF imputation) for subjects in the Maintenance Study are summarized by treatment group. Pairwise comparisons (mean [SD]) of each filgotinib treatment group versus respective placebo were as follows:

Filgotinib 200mg: 0.3 (2.86), placebo: 3.2 (3.01); least-square mean difference (SE):−2.8 (0.35), p < 0.0001

Filgotinib 100 mg: 1.2 (3.09), placebo: 1.7 (2.96); least-square mean difference (SE):−0.7 (0.38), p = 0 .065

SF-36

Physical Component Summary

Pairwise comparisons of (mean [SD]) change from maintenance baseline in SF-36 PCS scores for each filgotinib treatment group versus respective placebo were as follows:

Maintenance Week 15:

Filgotinib 200mg: 1.31 (6.216), placebo: −1.19 (6.740); LSM difference (SE):2.14 (0.653), p = 0.0012 Filgotinib 100 mg: 1.41 (6.896), placebo: −0.61 (6.120); LSM difference (SE):1.66 (0.690), p = 0.0171

Maintenance Week 47

Filgotinib 200mg: 2.45 (5.745), placebo: 1.90 (5.506); LSM difference (SE):2.01 (0.665), p = 0.0027 Filgotinib 100 mg: 1.45 (6.536), placebo: 1.68 (5.437); LSM difference (SE):0.72 (0.697), p = 0 .3037

Mental Component Summary

Maintenance Week 15

Filgotinib 200mg: 1.29 (9.139), placebo: −2.26 (8.722); LSM difference (SE):2.40 (0.885), p = 0.0071 Filgotinib 100 mg: 0.08 (7.651), placebo: −1.48 (8.401); LSM difference (SE):1.19 (0.844), p = 0.1607

Maintenance Week 47

Filgotinib 200mg: 1.45 (8.980), placebo: −0.99 (8.572); LSM difference (SE):2.62 (0.941), p = 0.0057 Filgotinib 100 mg: 1.44 (6.973), placebo: 1.86 (7.769); LSM difference (SE):0.04 (0.884), p = 0.962

EQ-5D

From maintenance baseline to maintenance Week15 and maintenance Week 47, the percentage of subjects who reported an improvement in the specific health dimensions were as follows:

Maintenance Week15

Mobility: filgotinib 200mg: 13.4%, placebo: 5.6%; filgotinib 100mg: 8.4%; placebo: 5.3%

Self-care: filgotinib 200mg: 1.2%, placebo:5.6%; filgotinib 100mg: 2.3%; placebo: 1.8%

Usual activities: filgotinib 200mg: 14.5%, placebo: 11.3%; filgotinib 100mg: 18.3%; placebo: 10.5%

Pain/discomfort: filgotinib 200mg: 19.8%, placebo: 14.1%; filgotinib 100mg: 22.9%; placebo: 15.8%

Anxiety/depression: filgotinib 200mg: 22.7%, placebo: 12.7%; filgotinib 100mg: 20.6%; placebo: 15.8%

Maintenance Week 47

Mobility: filgotinib 200mg: 13.4%, placebo: 10.0%; filgotinib 100mg: 8.0%; placebo: 7.5%

Self-care: filgotinib 200mg: 3.4%, placebo: 5.0%; filgotinib 100mg: 4.0%; placebo: 2.5%

Usual activities: filgotinib 200mg: 18.8%, placebo: 15.0%; filgotinib 100mg: 16.0%; placebo: 10.0%

Pain/discomfort: filgotinib 200mg: 23.5%, placebo: 22.5%; filgotinib 100mg: 23.0%; placebo: 17.5%

Anxiety/depression: filgotinib 200mg: 22.8%, placebo: 17.5%; filgotinib 100mg: 22.0%; placebo: 25.0%

EQ-VAS

Pairwise comparisons (mean[SD]) foreach filgotinib treatment group versus respective placebo were as follows:

Maintenance Week 15

Filgotinib 200mg: 3 (17.9) mm, placebo: −5 (18.1) mm; LSM difference (SE): 5 (1.8) mm, p = 0.0026. Filgotinib 100mg: 1 (17.1) mm, placebo: −4 (22.3) mm; LSM difference (SE): 3 (2.0) mm, p = 0.0944

Maintenance Week 47:

Filgotinib 200mg: 5 (17.0) mm, placebo: 1 (12.5) mm; LSM difference (SE): 5 (1.8) mm, p = 0.0030
Filgotinib 100mg: 2 (15.9) mm, placebo: 4 (14.6) mm; LSM difference (SE): 1 (1.8) mm, p = 0.4235

WPAI

Pairwise comparisons (mean [SD]) for each filgotinib treatment group versus respective placebo were as follows:

Absenteeism

Maintenance Week 15

Filgotinib 200mg: −2. 4 (14.97), placebo: 1.7 (29.87); LSM difference (SE):−4 .5 (2.42), p = 0.0664
Filgotinib 100 mg:−4.9 (22.10), placebo:−2.7 (17.84); LSM difference (SE):−1.1 (2.29), p = 0.6377

Maintenance Week 47

Filgotinib 200mg: −1.7 (22.49), placebo: −5.1 (37.20); LSM difference (SE):−3.4(2.94), p = 0.2425
Filgotinib 100 mg: −6.4 (22.91), placebo: −9.6 (29.45); LSM difference (SE):0.9 (2.45), p = 0.7038

Presenteeism

Maintenance Week 15

Filgotinib 200mg: −4 .5 (21.87), placebo: −2.4 (23.42); LSM difference (SE): −3 .1 (2. 72), p =0.2604 Filgotinib 100 mg: −8 .4 (22.22), placebo: 4.9 (26.05); LSM difference (SE): −8 .5 (2.68), p = 0.0017

Maintenance Week 47

Filgotinib 200mg: −7.4 (18.66), placebo: −0.6 (25.55); LSM difference (SE):−6.7(2.69), p = 0.0131
Filgotinib 100 mg: −10.0 (23.14), placebo: −5.2 (12.50); LSM difference (SE):−7.4 (2.77), p = 0.0085

Work Productivity Loss

Maintenance Week 15

Filgotinib 200mg: −6.0 (24.72), placebo: 3.5 (33.78); LSM difference (SE): −8 .6 (3.34), p = 0.0110
Filgotinib 100 mg: −8. 6 (28.65), placebo: 4.2 (27.64); LSM difference (SE): −9 .1 (3.23), p = 0.0056

Maintenance Week 47

Filgotinib 200mg: −6 .5 (25.66), placebo: −5.5 (36.88); LSM difference (SE):−9.0 (3 .66), p = 0.0145 Filgotinib 100 mg: −11.5 (27.97), placebo: −9.1 (16.36); LSM difference (SE):−7. 5 (3.30), p = 0.0250

Activity Impairment

Maintenance Week 15

Filgotinib 200mg: −3.0 (23.27), placebo: 4.8 (23.23); LSM difference (SE):−5.7(2.36), p = 0.0163
Filgotinib 100 mg: −4.4 (26.05), placebo: 6.3 (27.03); LSM difference (SE):−7.2 (2 .54), p = 0.0051

Maintenance Week 47

Filgotinib 200mg: −4 .2 (2 6.59), placebo: 1.3 (25.84); LSM difference (SE):−5 .7 (2 .55), p = 0.0260 Filgotinib 100 mg: −8 .8 (2 2.75), placebo: −6.8 (24.01); LSM difference (SE):−5 .3 (2.42), p = 0.0304

<u>IBDQ Subscale Scores</u>

Pairwise comparisons (mean [SD]) for each filgotinib treatment group versus respective placebo were as follows:

Bowel Symptoms

Maintenance Week15

Filgotinib 200mg: 0.2 (0.89), placebo: −0.5 (1.18); LSM difference (SE):0.4 (0.10), p < 0.0001
Filgotinib 100mg: 0.1 (0.99), placebo: −0.5 (1.26); LSM difference (SE):0.4 (0.11), p = 0.0011

Maintenance Week47

Filgotinib 200mg: 0.3 (0.94), placebo: −0.3 (0.96); LSM difference (SE):0.5 (0.11), p < 0.0001
Filgotinib 100mg: 0.1 (0.96), placebo: 0.0 (0.72); LSM difference (SE):0.2 (0 .12), p = 0.0609

Systemic Symptoms

Maintenance Week15

Filgotinib 200mg: 0.1 (0.96), placebo: −0.3 (1.03); LSM difference (SE):0.2 (0.10), p = 0.0157
Filgotinib 100mg: 0.1 (1. 06), placebo: −0.4 (1.21); LSM difference (SE):0.3 (0.11), p = 0.0042

Maintenance Week47

Filgotinib 200mg: 0.2 (0.86), placebo: 0.0 (0.92); LSM difference (SE):0.3 (0.10), p = 0.0049
Filgotinib 100mg: 0.2 (1.02), placebo: 0.2 (0.91); LSM difference (SE):0.2 (0 .12), p = 0.1477

Emotional Function

Maintenance Week15

Filgotinib 200mg: 0.2 (0.86), placebo: −0.3 (0.97); LSM difference (SE):0.3 (0.09), p = 0.0002
Filgotinib 100mg: 0.1 (0.91), placebo: −0.3 (1.10); LSM difference (SE):0.3 (0.11), p = 0.007

Maintenance Week47

Filgotinib 200mg: 0.3 (0.96), placebo: −0.2 (0.89); LSM difference (SE):0.4 (0.10), p = 0.0002
Filgotinib 100mg: 0.3 (0.80), placebo: 0.2 (0.76); LSM difference (SE):0.1 (0.11), p = 0.1798

Social Function

Maintenance Week15

Filgotinib 200mg: 0.3 (0.93), placebo: −0.4 (1.23); LSM difference (SE):0.5 (0.11), p < 0.0001
Filgotinib 100mg: 0.2 (1.14), placebo: −0.3 (1.34); LSM difference (SE):0.3 (0.13), p = 0.0129

Maintenance Week47

Filgotinib 200mg: 0.4 (1.11), placebo: 0.1 (0.96); LSM difference (SE):0.4 (0.12), p = 0.0004
Filgotinib 100mg: 0.4 (0.93), placebo: 0.3 (0.76); LSM difference (SE):0.2 (0.12), p = 0.0643

IBDQ Total Scores

Pairwise comparisons (mean [SD]) foreach filgotinib treatment group versus respective placebo were as follows:

Maintenance Week 15

Filgotinib 200mg: 5 (25.5), placebo: −12 (31.8); LSM difference (SE): 12 (2.9), p < 0.0001
Filgotinib 100 mg: 4 (29.1), placebo: −11 (35.6); LSM difference (SE): 10 (3.4), p = 0.0022

Maintenance Week 47

Filgotinib 200mg: 9 (27.3), placebo: −5 (26.5); LSM difference (SE):13 (3 .2), p < 0.0001
Filgotinib 100 mg: 8 (26.0), placebo:5 (21.5); LSM difference (SE): 6 (3.3), p = 0.0834

Ancillary analyses

Efficacy Analyses of Subgroups- Cohort A induction study

Forest plots of the treatment difference between the proportions of subjects who achieved EBS remission at Week 10 by stratification factors are presented for filgotinib 200 mg versus placebo and filgotinib 100 mg versus placebo in the figures below.

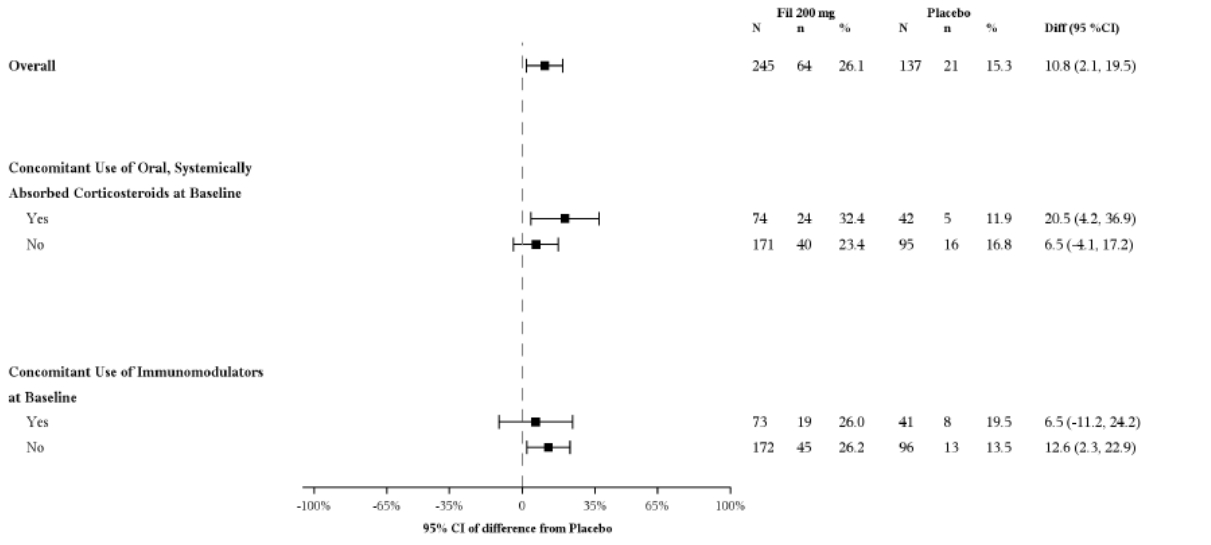


Figure 20 Forest plot of treatment difference between filgotinib 200mg and placebo in EBS remission at week 10 by stratification factors induction study: cohort A

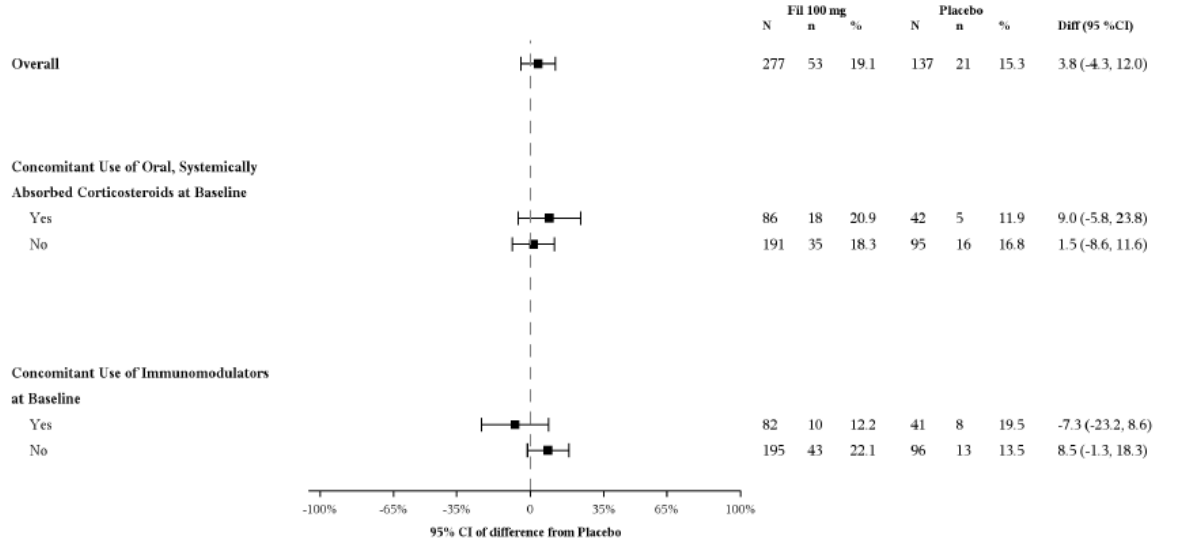


Figure 21 Forest plot of treatment difference between filgotinib 100mg and placebo in EBS remission at week 10 by stratification factors induction study: cohort A – full analysis set

Forest plots of the treatment difference between the proportions of subjects who achieved EBS remission at Week 10 by demographic factors are presented for filgotinib 200 mg versus placebo and filgotinib 100 mg versus placebo in the figures below.

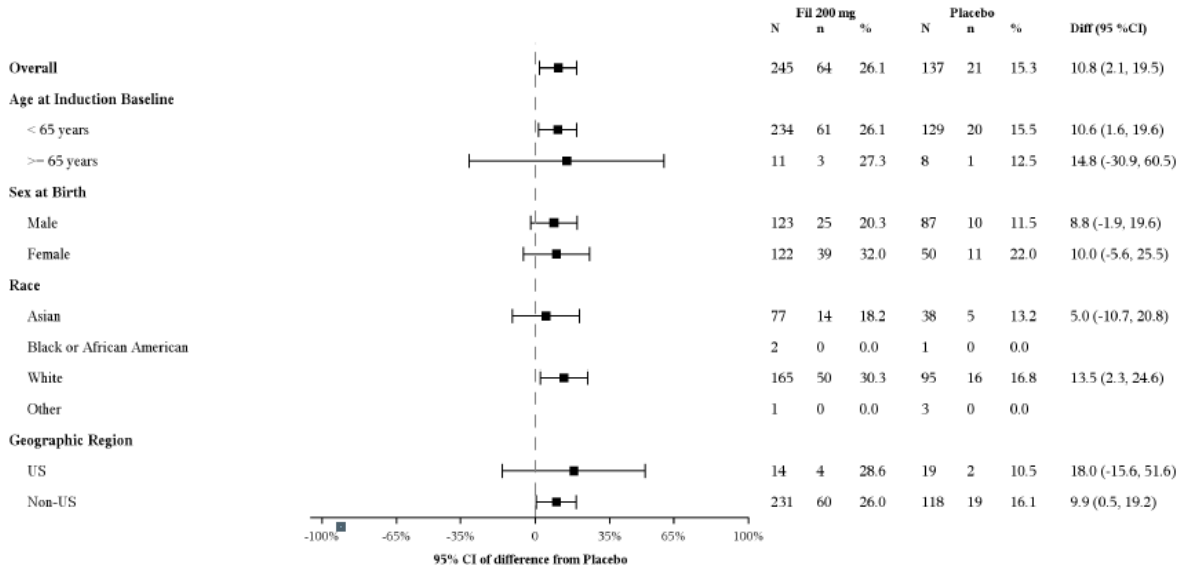


Figure 22 Forest plot of treatment difference between filgotinib 200mg and placebo in EBS remission at week 10 by demographics factors induction study: cohort A – full analysis set

Forest plots of the treatment difference between the proportions of subjects who achieved EBS remission at Week 10 by baseline disease characteristics are presented for filgotinib 200 mg versus placebo and filgotinib 100 mg versus placebo in Figure 15.9.1.14.3.1 and Figure 15.9.1.14.3.2, respectively.

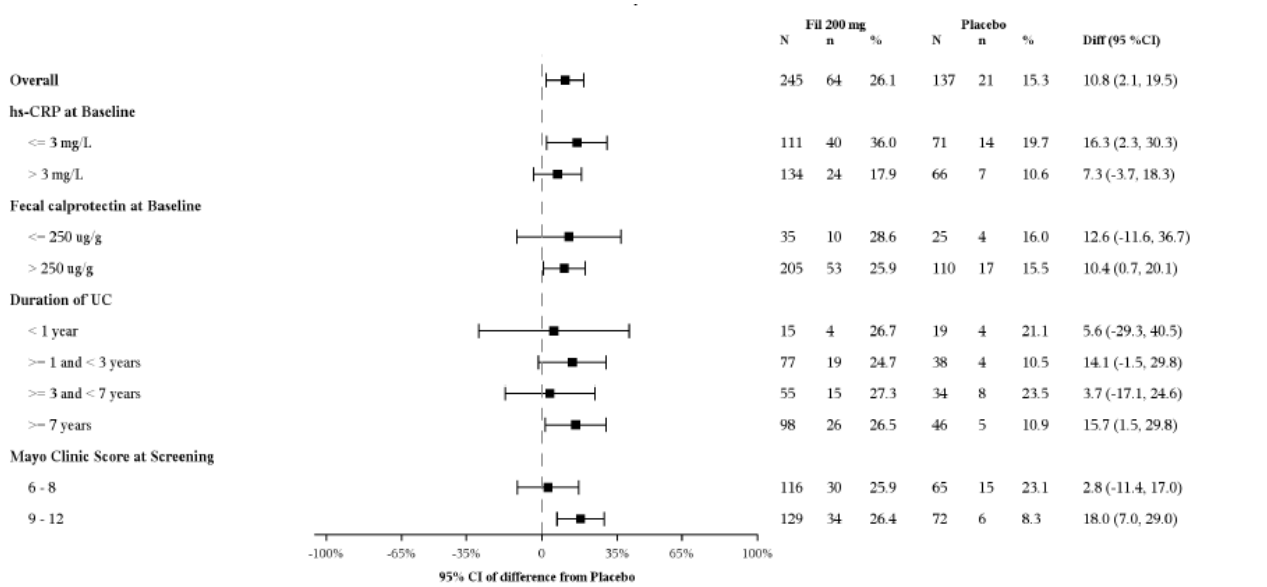


Figure 23 Forest plot of treatment difference between filgotinib 200mg and placebo in EBS remission at week 10 by disease characteristics induction study: cohort A

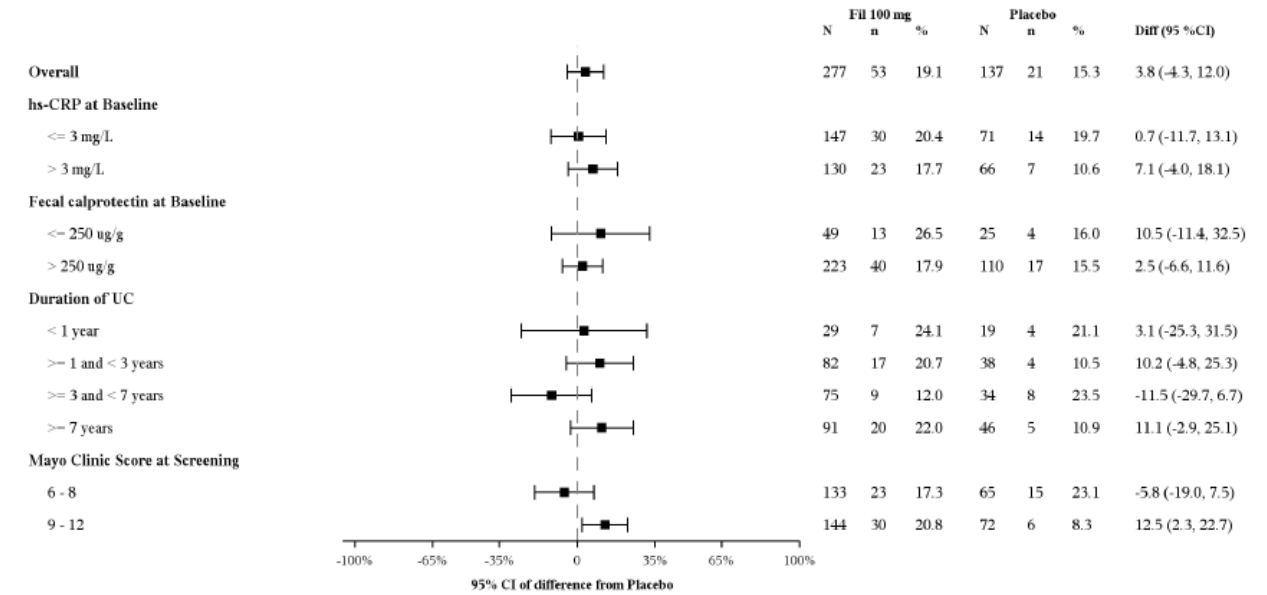


Figure 24 Forest plot of difference between filgotinib 100mg and placebo in EBS remission at week 10 by disease characteristics induction study: cohort A

Efficacy Analyses of Subgroups- Cohort B induction study

Forest plots of the treatment difference between the proportions of subjects who achieved EBS remission at Week 10 by stratification factors (exposure to one biologic agent versus more than one biologic agent, concomitant use of oral, systemic corticosteroids at baseline and concomitant use of immunomodulators at baseline) are presented for filgotinib 200 mg versus placebo and filgotinib 100 mg versus placebo in the figures below.

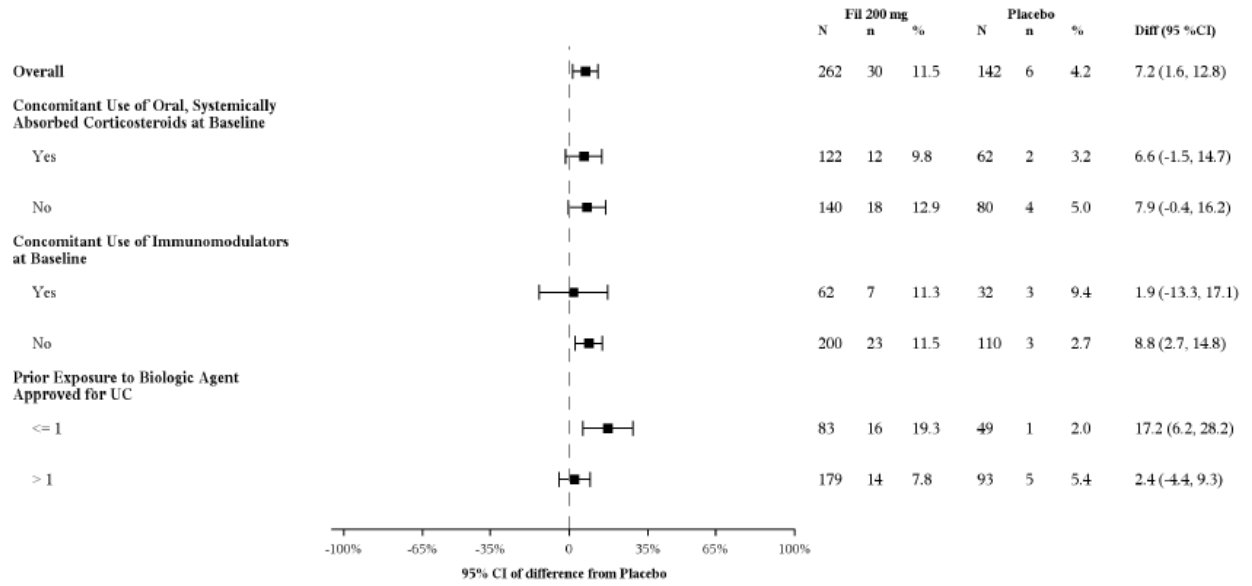


Figure 25 Forest plot of treatment difference between filgotinib 200mg and placebo in EBS remission at week 10 by stratification factors induction study: cohort B full analysis set

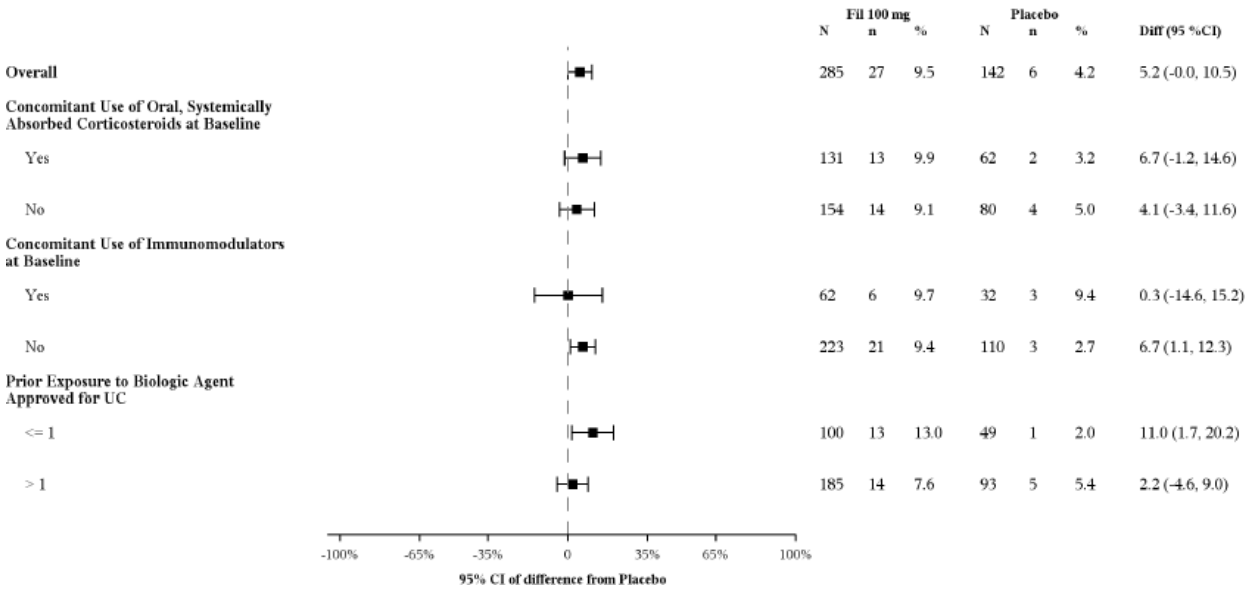


Figure 26 Forest plot of treatment difference between filgotinib 100mg and placebo in EBS remission at week 10 by stratification factors induction study: cohort B full analysis set

Forest plots of the treatment difference between the proportions of subjects who achieved EBS remission at Week 10 by demographic factors are presented for filgotinib 200 mg versus placebo and filgotinib 100 mg versus placebo in the figure below.

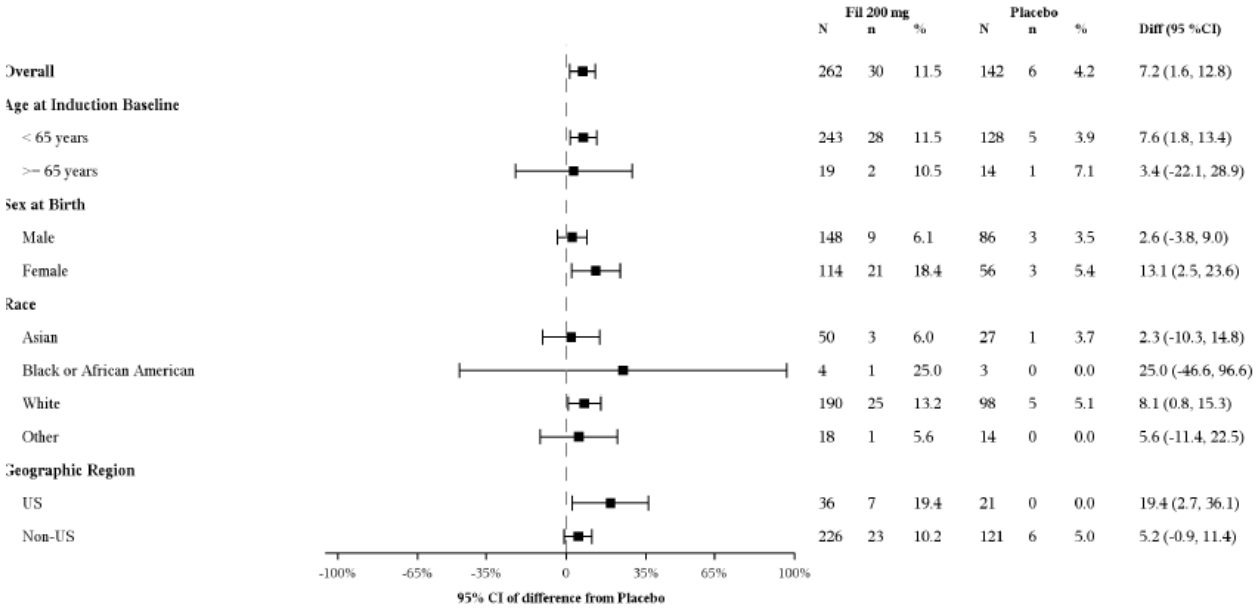


Figure 27 Forest plot of treatment difference between filgotinib 200mg and placebo in EBS remission at week 10 by demographic factors induction study: cohort B full analysis set

Forest plots of the treatment difference between the proportions of subjects who achieved EBS remission at Week 10 by baseline disease characteristics are presented for filgotinib 200 mg versus placebo and filgotinib 100 mg versus placebo in Figures below.

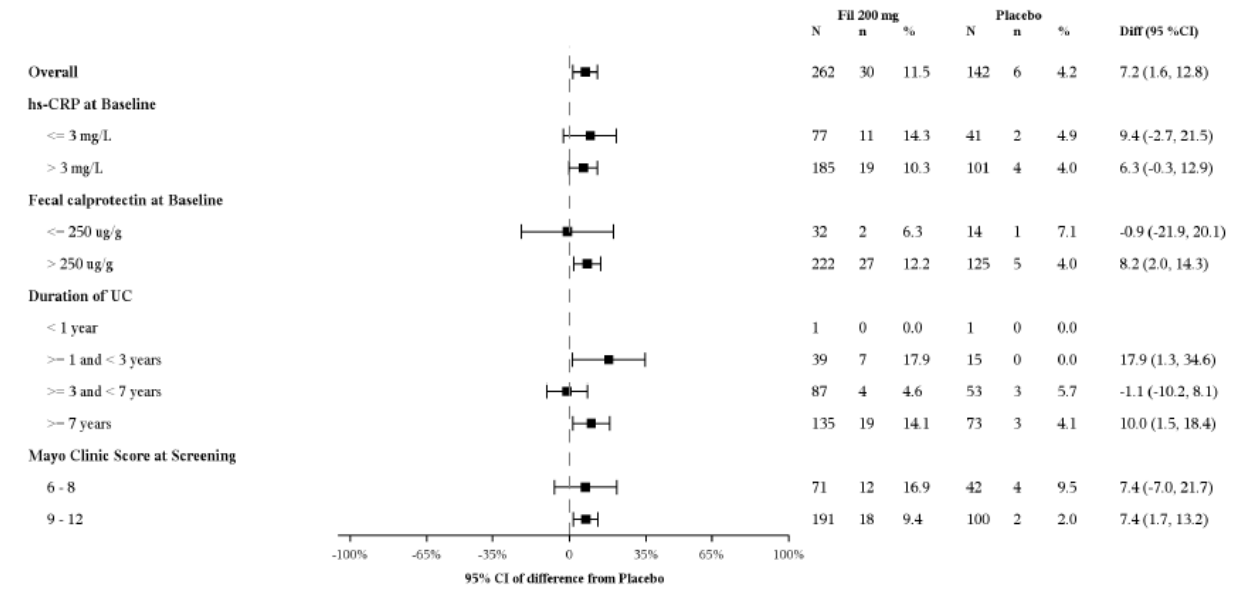


Figure 28 Forest plot of treatment difference between filgotinib 200mg and placebo in EBS remission at week 10 by disease characteristics induction study: cohort B full analysis set

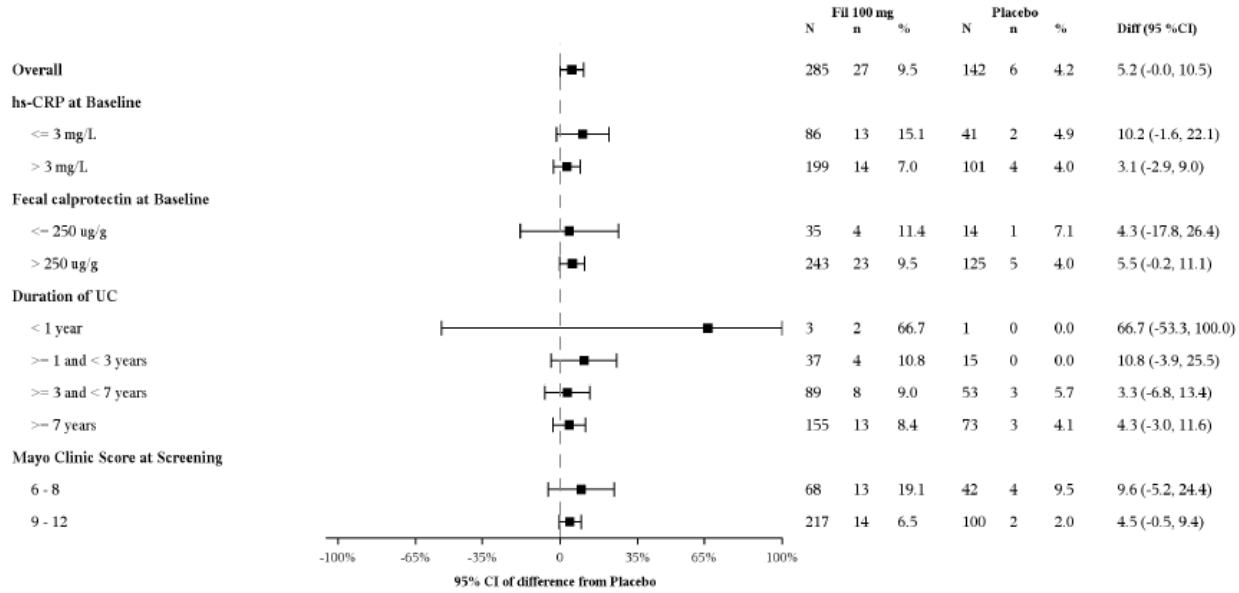


Figure 29 Forest plot of treatment difference between filgotinib 100mg and placebo in EBS remission at week 10 by disease characteristics induction study: cohort B full analysis set

Forest plots of the treatment difference between the proportions of subjects who achieved EBS remission at Week 10 by previous history of biologic agent are presented for filgotinib 200 mg versus placebo and filgotinib 100 mg versus placebo in Figures below.

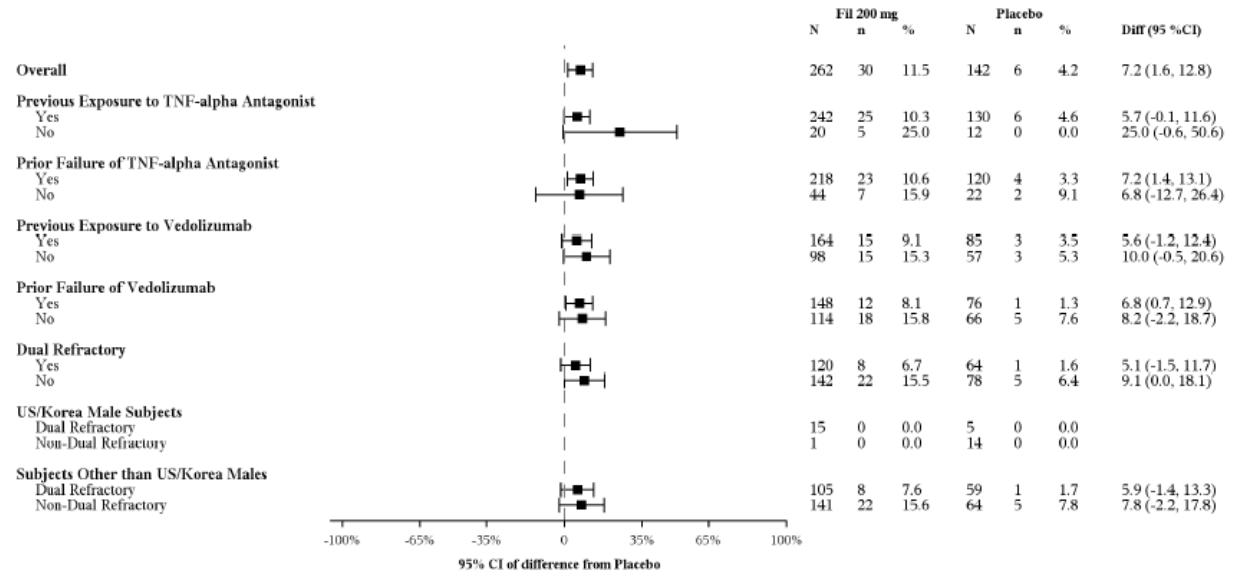


Figure 30 Forest plot of treatment difference between filgotinib 200mg and placebo in EBS remission at week 10 by biologic history induction study: cohort B full analysis set

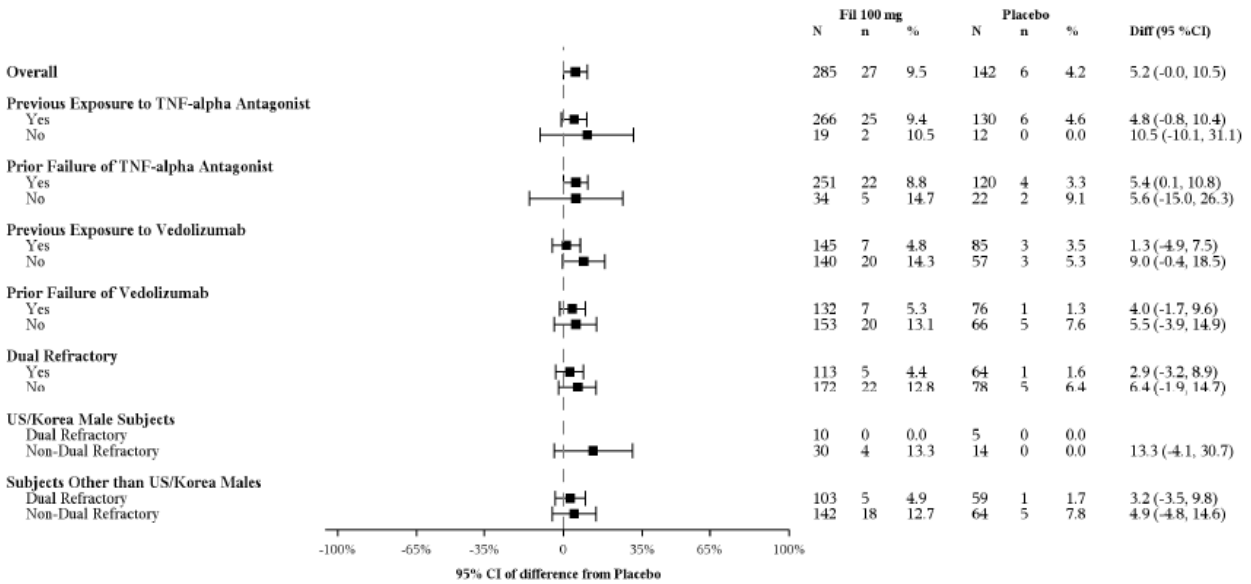
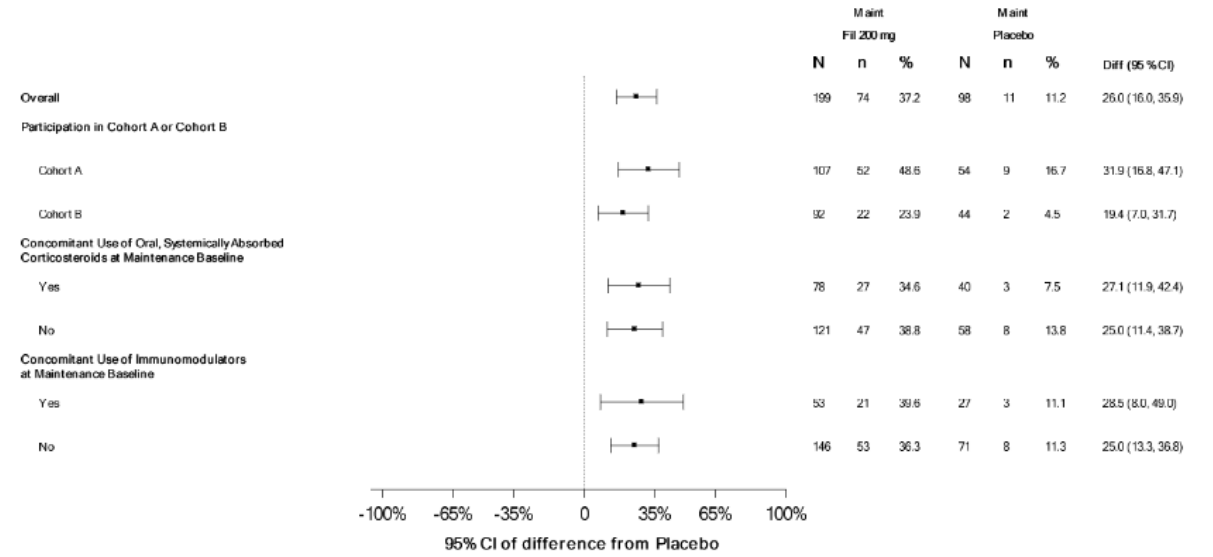


Figure 31 Forest plot of treatment difference between filgotinib 100mg and placebo in EBS remission at week 10 by biologic history induction study: cohort B full analysis set

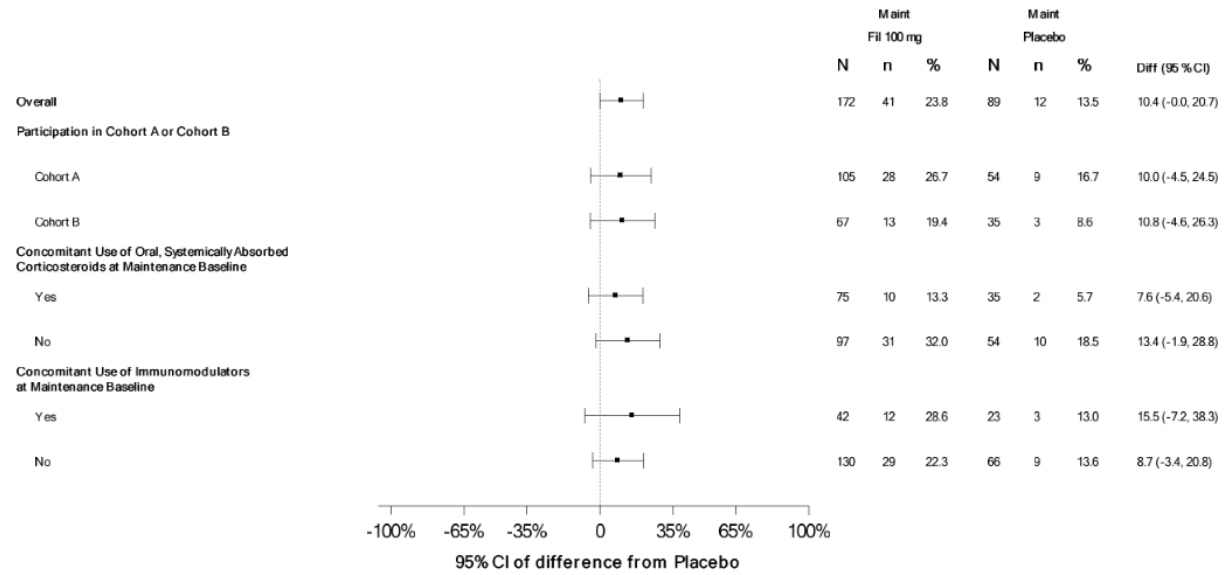
Efficacy Analyses of Subgroups – Maintenance Study

The primary efficacy endpoint was analysed by stratification and demographic factor subgroup.



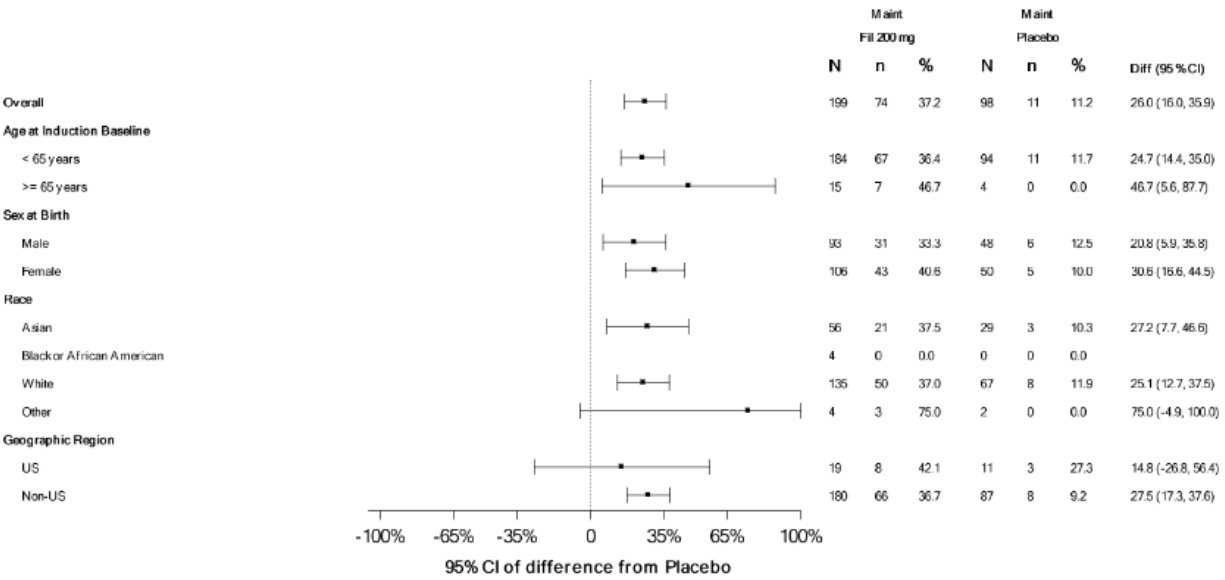
CI = confidence interval; Diff = difference; EBS = endoscopy/bleeding/stool frequency; Fil = filgotinib; Maint = Maintenance
Randomization stratum was based on clinical database value. EBS remission was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1-point decrease in stool frequency subscore from induction baseline to achieve 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction.

Figure 32 GS-US-418-3898: Forest Plot of Treatment Difference Between Filgotinib 200 mg and Placebo in EBS Remission at Week 58 by Stratification Factors, Maintenance Study (Full Analysis Set)



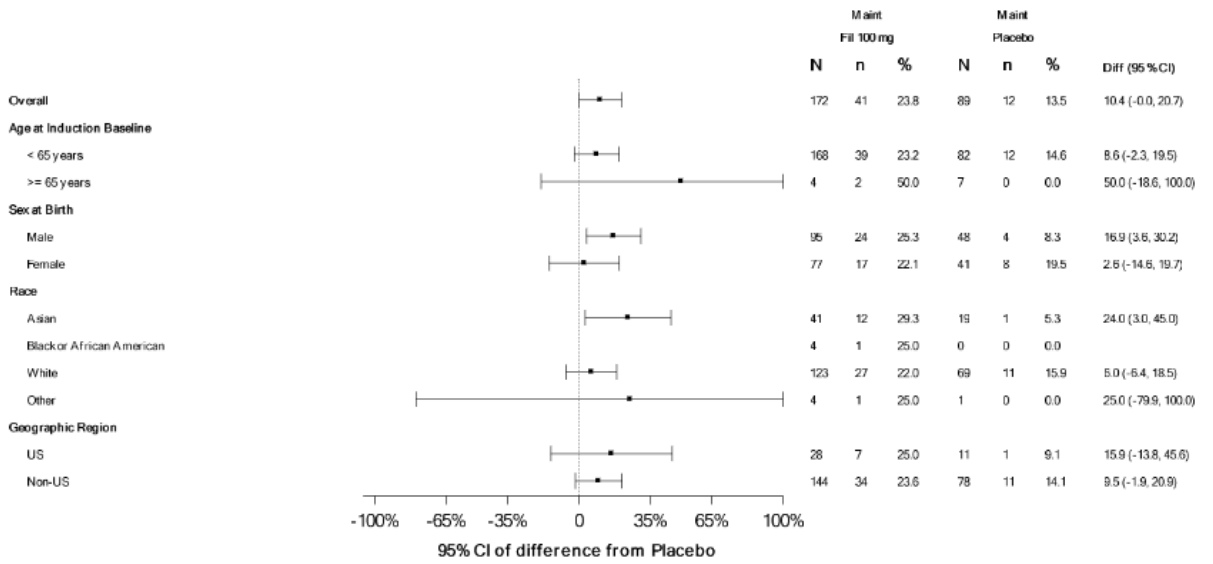
CI = confidence interval; Diff = difference; EBS = endoscopy/bleeding/stool frequency; Fil = filgotinib; Maint = Maintenance
Randomization stratum was based on clinical database value. EBS remission was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1-point decrease in stool frequency subscore from induction baseline to achieve 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction.

Figure 33 GS-US-418-3898: Forest Plot of Treatment Difference Between Filgotinib 100 mg and Placebo in EBS Remission at Week 58 by Stratification Factors, Maintenance Study (Full Analysis Set)



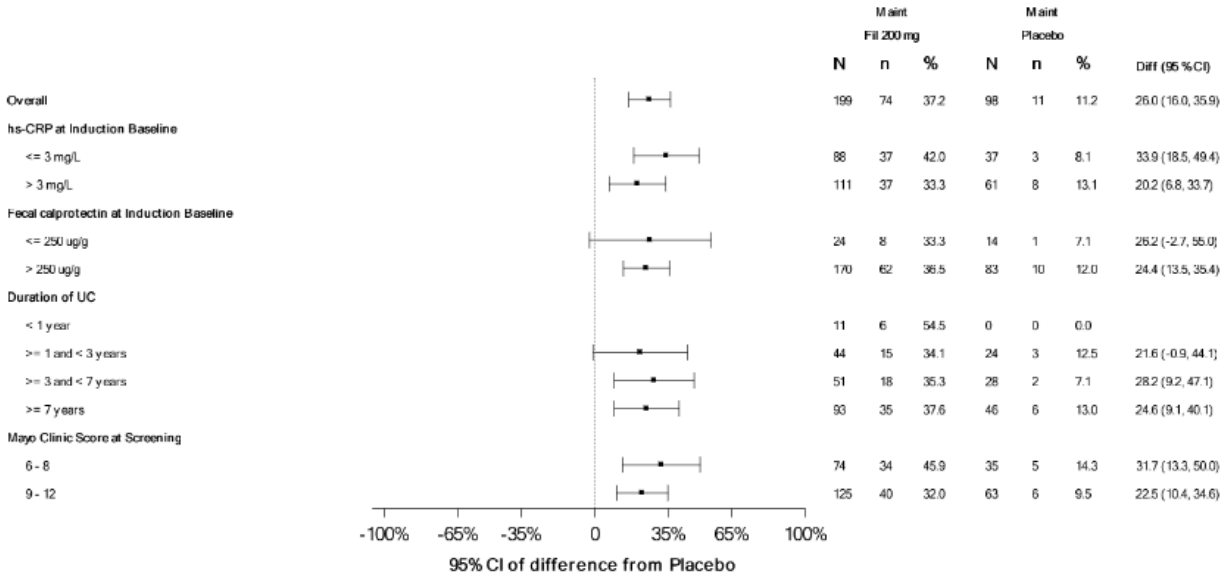
CI = confidence interval; Diff = difference; EBS = endoscopy/bleeding/stool frequency; Fil = filgotinib; Maint = Maintenance; US = United States
Randomization stratum was based on clinical database value. EBS remission was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1-point decrease in stool frequency subscore from induction baseline to achieve 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction.

Figure 34 GS-US-418-3898: Forest Plot of Treatment Difference Between Filgotinib 200 mg and Placebo in EBS Remission at Week 58 by Demographic Factors, Maintenance Study (Full Analysis Set)



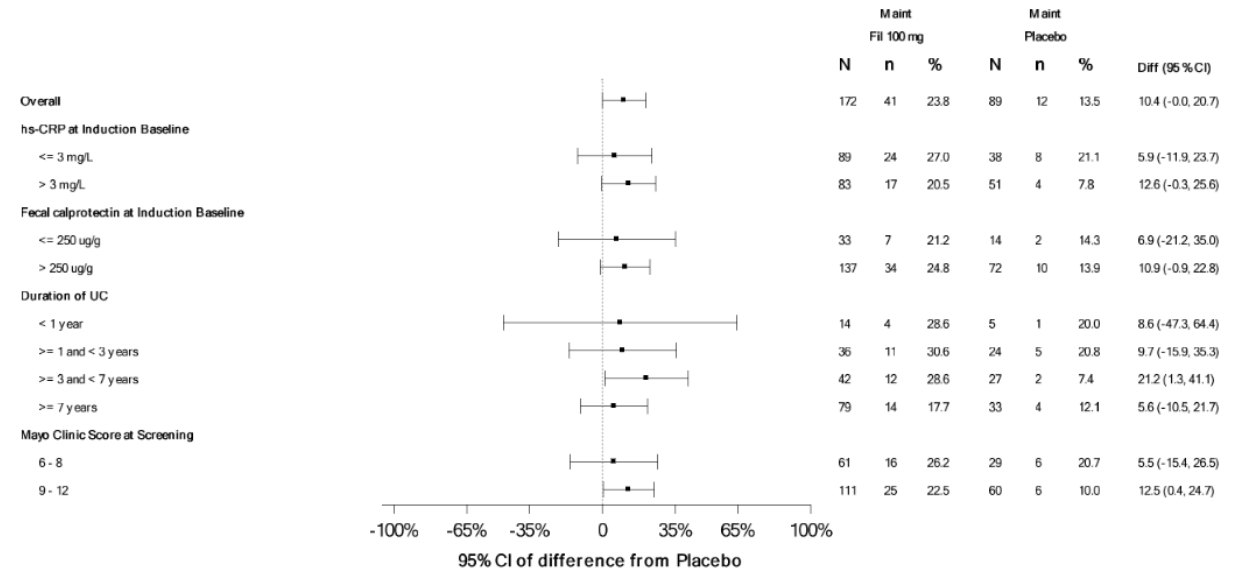
CI = confidence interval; Diff = difference; EBS = endoscopy/bleeding/stool frequency; Fil = filgotinib; Maint = Maintenance; US = United States
Randomization stratum was based on clinical database value. EBS remission is defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1-point decrease in stool frequency subscore from induction baseline to achieve 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction.

Figure 35 GS-US-418-3898: Forest Plot of Treatment Difference Between Filgotinib 100 mg and Placebo in EBS Remission at Week 58 by Demographic Factors, Maintenance Study (Full Analysis Set)



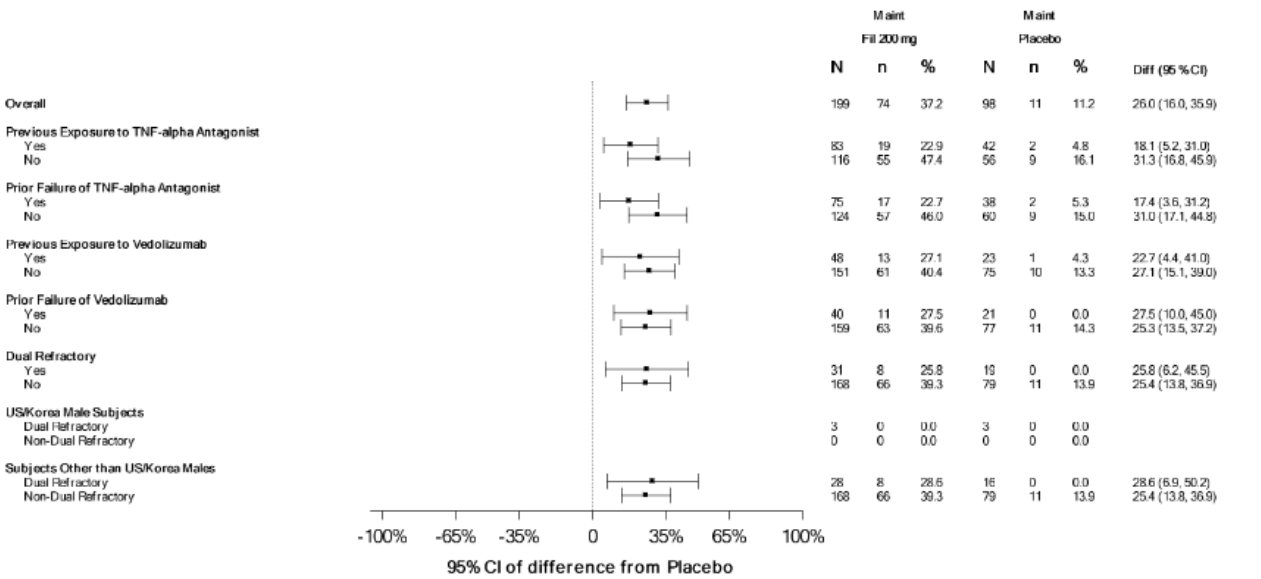
CI = confidence interval; Diff = difference; EBS = endoscopy/bleeding/stool frequency; Fil = filgotinib; hs-CRP =high-sensitivity C-reactive protein; Maint = Maintenance; UC = ulcerative colitis
Randomization stratum was based on clinical database value. EBS remission was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1-point decrease in stool frequency subscore from Induction baseline to achieve 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction.

Figure 36 GS-US-418-3898: Forest Plot of Treatment Difference Between Filgotinib 200 mg and Placebo in EBS Remission at Week 58 by Baseline Disease Characteristics, Maintenance Study (Full Analysis Set)



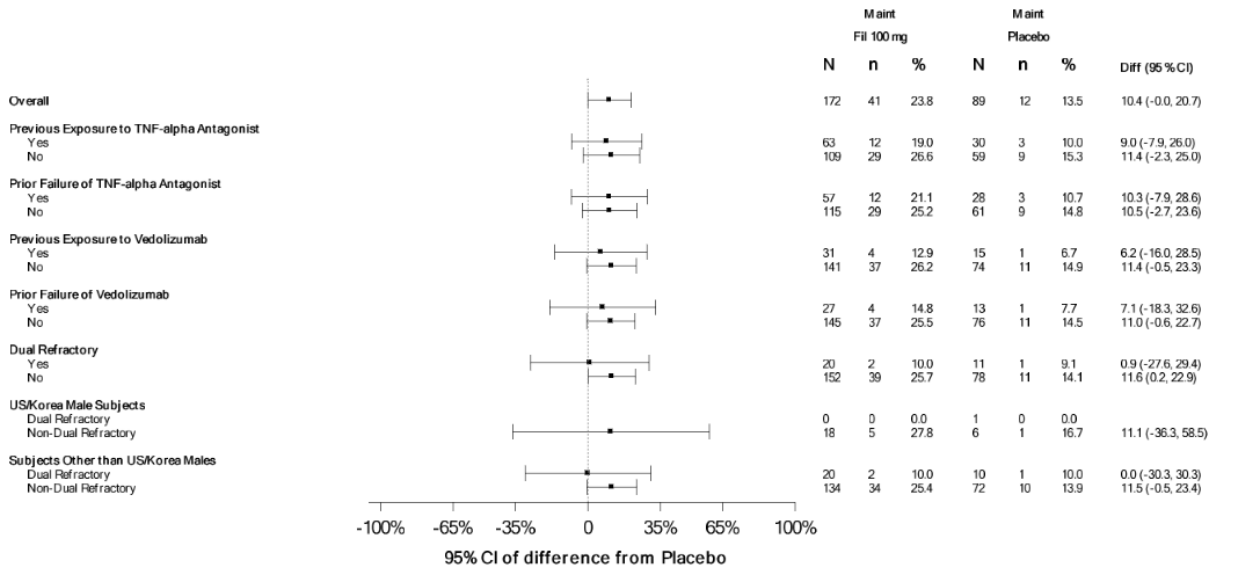
CI = confidence interval; Diff = difference; EBS = endoscopy/bleeding/stool frequency; Fil = filgotinib; hs-CRP =high-sensitivity C-reactive protein; Maint = Maintenance; UC = ulcerative colitis
Randomization stratum was based on clinical database value. EBS remission was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1-point decrease in stool frequency subscore from induction baseline to achieve 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction.

Figure 37 GS-US-418-3898: Forest Plot of Treatment Difference Between Filgotinib 100 mg and Placebo in EBS Remission at Week 58 by Baseline Disease Characteristics, Maintenance Study (Full Analysis Set)



CI = confidence interval; Diff = difference; EBS = endoscopy/bleeding/stool frequency; Fil = filgotinib; Maint = Maintenance; TNF = tumor necrosis factor; US = United States
Randomization stratum was based on clinical database value. EBS remission was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1-point decrease in stool frequency subscore from induction baseline to achieve 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction.
Dual refractory means having failed both TNF-alpha antagonist and vedolizumab treatment prior to induction baseline.

Figure 38 GS-US-418-3898: Forest Plot of Treatment Difference Between Filgotinib 200 mg and Placebo in EBS Remission at Week 58 by History of Prior Biologic Use, Maintenance Study (Full Analysis Set)



CI = confidence interval; Diff = difference; EBS = endoscopy/bleeding/stool frequency; Fil = filgotinib; Maint = Maintenance; TNF = tumor necrosis factor; US = United States
Randomization stratum was based on clinical database value. EBS remission was defined as having an endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1-point decrease in stool frequency subscore from induction baseline to achieve 0 or 1. The 95% CIs were calculated based on normal approximation with a continuity correction.
Dual refractory means having failed both TNF-alpha antagonist and vedolizumab treatment prior to induction baseline.

Figure 39 GS-US-418-3898: Forest Plot of Treatment Difference Between Filgotinib 100 mg and Placebo in EBS Remission at Week 58 by History of Prior Biologic Use, Maintenance Study (Full Analysis Set)

Summary of main study

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 45 Summary of Efficacy for trial GS-US-418-3898

Title: Combined Phase 2b/3, Double-Blind, Randomized, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Subjects with Moderately to Severely Active Ulcerative Colitis			
Study identifier	Study GS-US-418-3898 IND No.: 129647 EudraCT No.: 2016-001392-78 ClinicalTrials.gov Identifier: NCT02914522		
Design	Combined phase 2b/3, double-blind, randomized, placebo-controlled, parallel-group induction and maintenance studies		
	Duration of main phase:	Induction Studies: 11 weeks Maintenance Study: 47 weeks	
	Duration of run-in phase:	Not Applicable	
	Duration of extension phase:	At completion or if met discontinuation criteria, subjects had option to enroll in the long-term extension (LTE) Study GS-US-418-3899 (SELECTION LTE)	
Hypothesis	Superiority		
Treatment groups: Cohort A Induction Study	Filgotinib 200 mg	Number randomized = 245	
	Filgotinib 100 mg	Number randomized = 278	
	Placebo	Number randomized = 137	
Treatment groups: Cohort B Induction Study	Filgotinib 200 mg	Number randomized = 262	
	Filgotinib 100 mg	Number randomized = 286	
	Placebo	Number randomized = 143	
Treatments groups: Maintenance Study	Filgotinib 200 mg	Number randomized = 202	
	Filgotinib 100 mg	Number randomized = 179	
	Placebo	Number randomized = 283	
Endpoints and definitions: Cohort A Induction Study Cohort B Induction Study	Primary endpoint	Endoscopy/Bleeding/Stool frequency (EBS) remission at Week 10	An endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1 point decrease in stool frequency from baseline to achieve a subscore of 0 or 1 at Week 10
	Key secondary endpoints	Mayo Clinic Score (MCS) remission at Week 10	A MCS of 2 or less and no single subscore higher than 1 at Week 10
		Endoscopic subscore of 0 at Week 10	An endoscopic subscore of 0 at Week 10
		Geboes histologic remission at Week 10	Based on the Geboes Scale, all of the following must have been met to be considered in Geboes histologic remission at Week 10: Grade 0 of ≤ 0.3, Grade 1 of ≤ 1.1, Grade 2a of

			≤ 2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0
		MCS remission (alternative definition) at Week 10	Rectal bleed, stool frequency, and physician's global assessment subscores of 0 and an endoscopic subscore of 0 or 1; overall MCS of ≤ 1 at Week 10
Endpoints and definitions: Maintenance Study	Primary endpoint	EBS remission at Week 58	An endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1 point decrease in stool frequency from induction baseline to achieve a subscore of 0 or 1 at Week 58
	Key secondary endpoints	6-month corticosteroid-free EBS remission at Week 58	EBS remission with no corticosteroid use for the indication of UC for at least 6 months prior to Week 58 among subjects who are on corticosteroid at re-baseline (baseline of maintenance study). Subjects who weaned off steroids but required re-initiation within 6 months prior to Week 58 assessment were considered to have not met this endpoint
		Sustained EBS remission at Week 58	EBS remission at both Week 10 and Week 58
		MCS remission at Week 58	An MCS of 2 or less and no single subscore larger than 1 at Week 58
		Endoscopic subscore of 0 at Week 58	An endoscopic subscore of 0 at Week 58
		Geboes histologic remission at Week 58	Based on the Geboes Scale, all of the following must

				have been met to be considered in Geboes histologic remission at Week 58: Grade 0 of ≤ 0.3, Grade 1 of ≤ 1.1, Grade 2a of ≤ 2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0
		MCS remission (alternative definition) at Week 58		Rectal bleed, stool frequency, and physician's global assessment subscores of 0 and an endoscopic subscore of 0 or 1; overall MCS of ≤ 1 at Week 58
Database lock	06 May 2020 – Database Finalization and Treatment Unblinding			
Results and Analysis				
Analysis description	A stratified Cochran-Mantel-Haenszel test comparing filgotinib 200 mg or 100 mg vs. placebo on the proportion of subjects achieving the endpoint.			
Analysis population and time point description	Induction Studies: The Full Analysis Set (FAS) for each induction study included all randomized subjects who took at least 1 dose of study drug in the corresponding induction study.			
Descriptive statistics and estimate variability: Cohort A Induction Study	Treatment group	Filgotinib 200 mg	Filgotinib 100 mg	Placebo
	Number FAS	245	277	137
	EBS remission	26.1%	19.1%	15.3%
	95% CI	20.4%; 31.8%	14.3%; 23.9%	8.9%; 21.7%
	MCS remission	24.5%	17.0%	12.4%
	95% CI	18.9%; 30.1%	12.4%; 21.6%	6.5%; 18.3%
	Endoscopic subscore of 0	12.2%	5.8%	3.6%
	95% CI	7.9%; 16.6%	2.8%; 8.7%	0.1%; 7.2%
	Geboes histologic remission	35.1%	23.8%	16.1%
	95% CI	28.9%; 41.3%	18.6%; 29.0%	9.5%; 22.6%
	MCS remission (alternative definition)	12.2%	8.7%	4.4%
	95% CI	7.9%; 16.6%	5.2%; 12.2%	0.6%; 8.2%
Descriptive statistics and estimate variability: Cohort B Induction Study	Treatment group	Filgotinib 200 mg	Filgotinib 100 mg	Placebo
	Number FAS	262	285	142
	EBS remission	11.5%	9.5%	4.2%
	95% CI	7.4%; 15.5%	5.9%; 13.0%	0.6%; 7.9%
	MCS remission	9.5%	6.0%	4.2%
	95% CI	5.8%; 13.3%	3.0%; 8.9%	0.6%; 7.9%
	Endoscopic subscore of 0	3.4%	2.1%	2.1%
	95% CI	1.0%; 5.8%	0.3%; 3.9%	0.0%; 4.8%
	Geboes histologic remission	19.8%	13.7%	8.5%
	95% CI	14.8%; 24.9%	9.5%; 17.8%	3.5%; 13.4%
	MCS remission (alternative definition)	3.8%	2.1%	2.1%

	95% CI	1.3%; 6.3%		0.3%; 3.9%	0.0%; 4.8%
Analysis population and time point description	Maintenance Study: FAS for the Maintenance Study included all subjects randomized to either the filgotinib 200 mg or filgotinib 100 mg treatment groups in the induction studies who achieved EBS remission or MCS response at Week 10, were rerandomized, and took at least 1 dose of study drug in the Maintenance Study.				
Descriptive statistics and estimate variability: Maintenance Study	Treatment group	Filgotinib 200 mg	Respective placebo	Filgotinib 100 mg	Respective placebo
	Number FAS	199	98	172	89
	EBS remission	37.2%	11.2%	23.8%	13.5%
	95% CI	30.2%; 44.2%	4.5%; 18.0%	17.2%; 30.5%	5.8%; 21.1%
	6-month corticosteroid-free EBS remission	27.2%	6.4%	13.6%	5.4%
	95% CI	17.5%; 36.8%	0.0%; 14.4%	5.5%; 21.7%	0.0%; 14.0%
	Sustained EBS remission	18.1%	5.1%	8.7%	7.9%
	95% CI	12.5%; 23.7%	0.2%; 10.0%	4.2%; 13.2%	1.7%; 14.0%
	MCS remission	34.7%	9.2%	22.7%	13.5%
	95% CI	27.8%; 41.5%	3.0%; 15.4%	16.1%; 29.2%	5.8%; 21.1%
	Endoscopic subscore of 0	15.6%	6.1%	13.4%	7.9%
	95% CI	10.3%; 20.9%	0.9%; 11.4%	8.0%; 18.7%	1.7%; 14.0%
	Geboes histologic remission	38.2%	13.3%	27.9%	18.0%
	95% CI	31.2%; 45.2%	6.0%; 20.5%	20.9%; 34.9%	9.4%; 26.5%
	MCS remission (alternative definition)	22.1%	6.1%	12.2%	7.9%
	95% CI	16.1%; 28.1%	0.9%; 11.4%	7.0%; 17.4%	1.7%; 14.0%
Effect estimate per comparison: Cohort A Induction Study	Primary endpoint: EBS remission	Comparison groups	Filgotinib 200 mg vs placebo		
		Difference	10.8%		
		95% CI	2.1%; 19.5%		
		P-value	0.0157		
	Primary endpoint: EBS remission	Comparison groups	Filgotinib 100 mg vs placebo		
		Difference	3.8%		
		95% CI	−4.3%; 12.0%		
		P-value	0.3379		
	Key secondary endpoint: MCS remission	Comparison groups	Filgotinib 200 mg vs placebo		
		Difference	12.1%		
		95% CI	3.8%; 20.4%		
		P-value	0.0053		
	Key secondary endpoint: MCS remission	Comparison groups	Filgotinib 100 mg vs placebo		
		Difference	4.6%		
		95% CI	−3.1%; 12.2%		
		P-value	0.2295		
	Key secondary endpoint: Endoscopic subscore of 0	Comparison groups	Filgotinib 200 mg vs placebo		
		Difference	8.6%		
		95% CI	2.9%; 14.3%		
		P-value	0.0047		
	Key secondary endpoint: Endoscopic subscore of 0	Comparison groups	Filgotinib 100 mg vs placebo		
		Difference	2.1%		
		95% CI	−2.6%; 6.8%		
		P-value	0.3495		

	Key secondary endpoint: Geboes histologic remission	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	19.0%
		95% CI	9.9%; 28.2%
		P-value	< 0.0001
	Key secondary endpoint: Geboes histologic remission	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	7.8%
		95% CI	−0.7%; 16.2%
		P-value	0.0672
	Key secondary endpoint: MCS remission (alternative definition)	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	7.9%
		95% CI	1.9%; 13.8%
		P-value	0.0105
	Key secondary endpoint: MCS remission (alternative definition)	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	4.3%
		95% CI	−1.0%; 9.6%
		P-value	0.1062
Effect estimate per comparison: Cohort B Induction Study	Primary endpoint: EBS remission	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	7.2%
		95% CI	1.6%; 12.8%
		P-value	0.0103
	Primary endpoint: EBS remission	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	5.2%
		95% CI	−0.0%; 10.5%
		P-value	0.0645
	Key secondary endpoint: MCS remission	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	5.3%
		95% CI	−0.1%; 10.7%
		P-value	0.0393
	Key secondary endpoint: MCS remission	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	1.7%
		95% CI	−3.1%; 6.6%
		P-value	0.5308
	Key secondary endpoint: Endoscopic subscore of 0	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	1.3%
		95% CI	−2.5%; 5.1%
		P-value	0.4269
	Key secondary endpoint: Endoscopic subscore of 0	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	−0.0%
		95% CI	−3.4%; 3.4%
		P-value	0.9987
	Key secondary endpoint: Geboes histologic remission	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	11.4%
		95% CI	4.2%; 18.6%
		P-value	0.0019
	Key secondary endpoint: Geboes Histologic Remission	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	5.2%
		95% CI	−1.4%; 11.8%
		P-value	0.1286

	Key secondary endpoint: MCS remission (alternative definition)	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	1.7%
		95% CI	−2.2%; 5.6%
		P-value	0.3084
	Key secondary endpoint: MCS remission (alternative definition)	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	−0.0%
		95% CI	−3.4%; 3.4%
		P-value	0.9109
Effect estimate per comparison: Maintenance Study	Primary endpoint: EBS remission	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	26.0%
		95% CI	16.0%; 35.9%
		P-value	< 0.0001
	Primary endpoint: EBS remission	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	10.4%
		95% CI	−0.0%; 20.7%
		P-value	0.0420
	Key secondary endpoint: 6-Month corticosteroid-free EBS remission	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	20.8%
		95% CI	7.7%; 33.9%
		P-value	0.0055
	Key secondary endpoint: 6-Month corticosteroid-free EBS remission	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	8.2%
		95% CI	−4.2%; 20.6%
		P-value	0.1265
	Key secondary endpoint: Sustained EBS remission	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	13.0%
		95% CI	5.3%; 20.6%
		P-value	0.0024
	Key secondary endpoint: Sustained EBS remission	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	0.9%
		95% CI	−7.0%; 8.7%
		P-value	0.7951
	Key secondary endpoint: MCS remission	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	25.5%
		95% CI	16.0%; 35.0%
		P-value	< 0.0001
	Key secondary endpoint: MCS remission	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	9.2%
		95% CI	−1.1%; 19.5%
		P-value	0.0658
	Key secondary endpoint: Endoscopic subscore of 0	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	9.5%
		95% CI	1.8%; 17.1%
		P-value	0.0157
	Key secondary endpoint: Endoscopic subscore of 0	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	5.5%
		95% CI	−2.9%; 13.9%
		P-value	0.1808

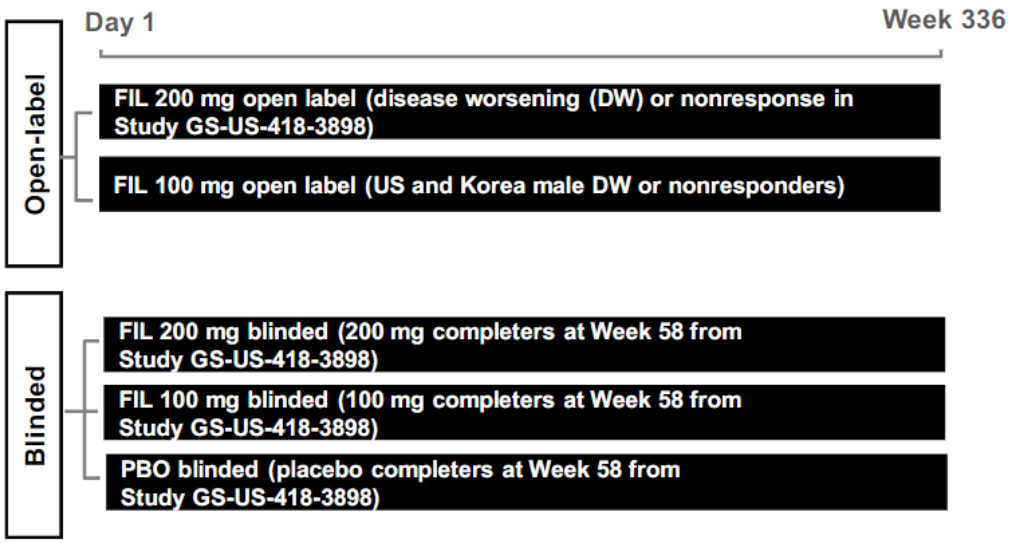
	Key secondary endpoint: Geboes histologic remission	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	24.9%
		95% CI	14.6%; 35.2%
		P-value	< 0.0001
	Key secondary endpoint: Geboes histologic remission	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	9.9%
		95% CI	−1.3%; 21.2%
		P-value	0.0521
	Key secondary endpoint: MCS remission (alternative definition)	Comparison groups	Filgotinib 200 mg vs placebo
		Difference	16.0%
		95% CI	7.8%; 24.2%
		P-value	0.0005
	Key secondary endpoint: MCS remission (alternative definition)	Comparison groups	Filgotinib 100 mg vs placebo
		Difference	4.3%
		95% CI	−3.9%; 12.6%
		P-value	0.2946

Clinical studies in special populations

No dedicated studies in special populations were performed this is considered acceptable by the CHMP.

Supportive study

GS-US-418 -3899: A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Ulcerative Colitis



DW = disease worsening; EBS = endoscopy/bleeding/stool frequency; FIL = filgotinib; MCS = Mayo Clinic Score; PBO = placebo; US = United States
Nonresponders were subjects who achieved neither EBS nor MCS response at Week 10 in Study GS-US-418-3898.
Subjects in Study GS-US-418-3898 who met disease worsening criteria were to be offered open-label filgotinib in Study GS-US-418-3899.
After Study GS-US-418-3898 was unblinded, Study GS-US-418-3899 was unblinded. After unblinding, subjects who were receiving blinded placebo were discontinued and subjects who were receiving blinded filgotinib continued on the same dose (as received when blinded) of open-label filgotinib dosing.

Figure 40 GS-US-418-3899 Study Design

Event	Date
First Subject Enrolled	23 February 2017
Last Subject Last Observation for this Report	28 February 2020
Database Finalization for Interim Analysis	05 May 2020
Treatment Unblinding	06 May 2020

Figure 41 GS-US-418-3899: Key Dates

This is an ongoing long-term extension study in adult male and female subjects with UC who had completed or discontinued Study GS-US-418-3898 due to protocol-specified efficacy discontinuation criteria. The study was designed to evaluate the safety, efficacy, association of clinical response with inflammatory biomarkers, and health-related quality of life (HRQoL) of filgotinib in subjects with moderately to severely active UC. The treatment administered (oral tablet) in Study GS-US-418-3899 depended on whether the subject completed, had disease worsening, or was a non-responder in Study GS-US-418-3898.

Subjects who completed Study GS-US-418-3898 continued blinded dosing at the same dosing regimen in Study GS-US-418-3899; filgotinib 200 mg, filgotinib 100 mg, or placebo once daily. After unblinding, subjects who were receiving blinded placebo were discontinued and subjects who were receiving blinded filgotinib continued the same dose of open label filgotinib.

Subjects who exited Study GS-US-418-3898 due to disease worsening or failure to meet response or remission criteria at Week 10 received open-label filgotinib 200 mg in Study GS-US-418-3899. The exception to this was males in the United States and Korea with disease worsening or failure to meet response criteria who were not dual refractory (having failed any tumour necrosis factor-alpha antagonist and vedolizumab); these male subjects received open-label filgotinib 100 mg in Study GS-US-418-3899.

A total of 1164 subjects were enrolled in the study and 1161 subjects received at least 1dose of study drug. As of the data cut-off date (28 February 2020), 347 subjects (29.9%) had prematurely discontinued study drug.

Objectives:

The primary objective of this study was:

- To observe the long-term safety of filgotinib in subjects who have completed or met protocol-specified efficacy discontinuation criteria in a prior Gilead-sponsored filgotinib treatment study in UC

The secondary objective of this study was:

- To evaluate the effect of filgotinib on partial Mayo Clinic Score (MCS)

The exploratory objectives of this study were:

- To evaluate the association of clinical response (based on partial MCS) on systemic or localized inflammatory biomarkers (eg, including but not limited to high-sensitivity C- reactive protein (hs- CRP), faecal calprotectin, faecal lactoferrin, and faecal MMP-9
- To evaluate health-related quality of life (HRQoL)

Statistical Methods:

A planned interim analysis was performed when this study was unblinded. No formal hypothesis testing was planned, and there was no sample size calculation. All subjects who had completed or met protocol-specified efficacy discontinuation criteria in Study GS-US-418-3898 were eligible to enrol, provided they also met the LTE study eligibility criteria.

The Safety Analysis Set was the primary analysis set for all efficacy and safety analyses, which included all enrolled subjects who received at least 1 dose of study drug. The secondary endpoint for this study was change from baseline in partial MCS. Descriptive statistics were used to summarize absolute values and change from baseline values in partial MCS by analysis visit and treatment group using observed values only. Exploratory endpoints for HRQoL included the change from baseline in SF-36, EQ-5D, IBDQ, and percent impairment in WPAI.

SUMMARY OF RESULTS

Table 46 *GS-US-418-3899: Disposition of Subjects (All Enrolled Analysis Set)*

	Filgotinib 200 mg	Filgotinib 100 mg	Placebo	Total
All Enrolled Subjects	873	158	133	1164
Safety Analysis Set	871	157	133	1161
Biomarker Analysis Set	716	112	94	922
Study Drug Completion Status				
Continuing Study Drug	601 (69.0%)	101 (64.3%)	112 (84.2%)	814 (70.1%)
Completed Study Drug	0	0	0	0
Prematurely Discontinued Study Drug	270 (31.0%)	56 (35.7%)	21 (15.8%)	347 (29.9%)
Reason for Premature Discontinuation of Study Drug				
Adverse Event	124 (14.2%)	33 (21.0%)	13 (9.8%)	170 (14.6%)
Investigator's Discretion	79 (9.1%)	5 (3.2%)	2 (1.5%)	86 (7.4%)
Subject Decision	63 (7.2%)	15 (9.6%)	6 (4.5%)	84 (7.2%)
Non-Compliance with Study Drug	2 (0.2%)	1 (0.6%)	0	3 (0.3%)
Lost to Follow-Up	0	2 (1.3%)	0	2 (0.2%)
Death	1 (0.1%)	0	0	1 (< 0.1%)
Protocol Violation	1 (0.1%)	0	0	1 (< 0.1%)

TNF = tumor necrosis factor; US = United States
All Enrolled Subjects were grouped according to the treatment assigned. Subjects who fully completed Study GS-US-418-3898 blinded were assigned blinded dosing with the same regimen in this study. Subjects who met protocol-specified efficacy discontinuation criteria in Study GS-US-418-3898 were assigned open-label filgotinib 200 mg, with the exception of US and Korea males who were not considered dual refractory (having failed any TNF alpha antagonist and vedolizumab); those males were assigned open-label filgotinib 100 mg.
Subjects in the Safety Analysis Set were summarized according to the treatment received. Only subjects from Safety Analysis Set were included for the study drug completion status summary. Percentages were calculated based on the number of subjects in the Safety Analysis Set.

In the Safety Analysis Set, the mean (SD) age of subjects was 44 (13.6) years. The majority of subjects were <65 years old (92.8%), male (59.2%), and most subjects were white (70.5%) or Asian (24.3%). Overall, most subjects (87.2%) were from countries outside of the US.

The mean (SD) partial MCS at baseline by treatment groups was as follows:

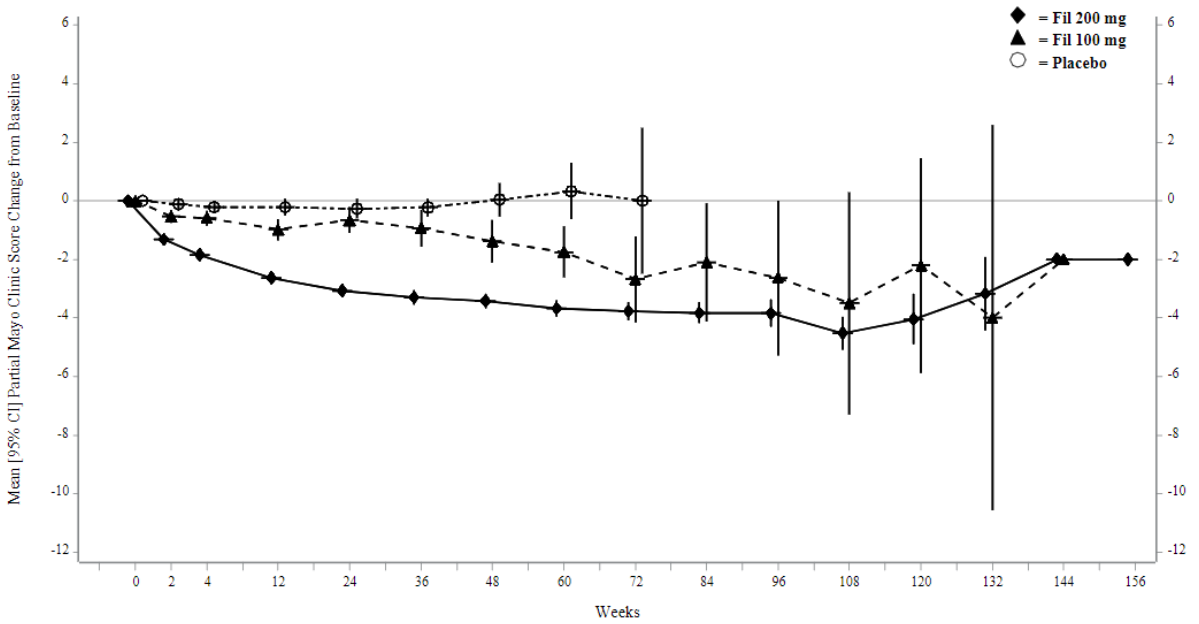
- filgotinib 200 mg, 5.1 (2.47)
- filgotinib 100 mg, 2.8 (2.57)

- and placebo, 1.5 (1.34).

The mean (SD) faecal calprotectin at baseline for the filgotinib200 mg, filgotinib 100 mg, and placebo were 1872 (3074.0) µg/g, 903 (1271.0) µg/g, 500 (789.3) µg/g, respectively.

The mean (SD) hs-CRP at baseline for the filgotinib200 mg, filgotinib 100 mg, and placebo were 7.93 (14.777) mg/L, 6.25 (11.920) mg/L, and 4.09 (7.776) mg/L, respectively.

Overall, 224 subjects (19.3%) were on systemic corticosteroids only, 224 subjects (19.3%) were on immunomodulators only, and 60 subjects (5.2%) were on both systemic corticosteroids and immunomodulators.



Fil 200 mg (n=):	848	801	801	761	662	584	478	369	283	207	117	62	24	6	1	1
Fil 100 mg (n=):	150	143	133	118	102	69	48	39	22	10	8	6	5	3	1	
Placebo (n=):	127	119	116	98	87	58	42	15	3							

Partial Mayo clinic score is the sum of rectal bleeding, stool frequency, and physician's global assessment subscores.
Source: Table 15.9.1, Listings 16.2.6.1.1 and 16.2.6.1.2

Figure 42 GS-US-418-3899: Mean (95% CI) Partial Mayo Clinic Score Change from Baseline by Visit (Safety Analysis Set)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

With this submission, the MAH seeks to add a new indication for Jyseleca (filgotinib) for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent. This application is supported by data from one phase 2b/3 study, GS-US-418-3898 (SELECTION), which was a double-blind, randomised, placebo-controlled multi-centre study that consisted of two induction studies and one randomised withdrawal maintenance study. Although the EMA Guideline (CHMP/EWP/18463/2006 Rev.1) on the development of new medicinal products for the treatment of Ulcerative Colitis states that "*to fulfil a claim for the treatment of ulcerative colitis, it is expected that at least two confirmatory trials are provided*", the two induction studies in the GS-US-418-3898

(SELECTION) study are conducted in two separate cohorts and thus, the CHMP considered that they can be acceptable to fulfil the requirements.

An additional long-term extension study GS-US-418-3899 is currently ongoing.

Dose response study

No dose finding studies were performed in patients with UC. The doses selected in the phase 2b/3 pivotal study in UC are justified on the basis of three elements:

- Results from a Phase 2 Study in patients with established, clinically active Crohn's disease, combined with the assumption that the targeted inflammatory pathways are similar between CD and UC.
- Exposure-Response analysis using data from the phase 2b/3 study in patients with moderately to severely active UC
- Efficacy and safety results from the phase 2b/3 study in patients with moderately to severely active UC

The CHMP considered that the overall data on the Phase 2 Study in patients with Crohn's disease are limited. Only one dose of filgotinib (200 mg QD) was evaluated in the first part of the study which was adequately powered to detect a treatment difference versus placebo at Week 10. In addition, the 100 mg QD dose was evaluated in the second part of the study only. However, this part was not powered to detect a treatment difference versus placebo, nor a treatment difference between the two filgotinib doses (100 mg QD and 200 mg QD). The results are only exploratory so a proper assessment of the treatment effect of the 100 mg QD dose cannot be made. Finally, the assumption that the targeted inflammatory pathways are similar between CD and UC cannot be definitely endorsed by the CHMP.

With respect to the Exposure-Response analysis, the MAH explored two doses only. In addition, no exposure-efficacy relationship was observed for the primary or key secondary endpoints in the induction studies and the maintenance study when analyses were conducted by dose. A lack of a consistent exposure-safety relationship was observed across doses or by dose. Exposure-efficacy analyses using combined data from the two filgotinib doses showed a positive trend for correlation between the AUC_{eff} quartile groups and the proportions of patients who achieved endoscopy/bleeding/stool frequency (EBS) remission in the induction studies and the maintenance study. Overall, the CHMP was of the opinion no relevant conclusion can be drawn regarding the adequate dose based on those data.

However, the efficacy and safety results of the pivotal phase 2b/3 study GS-US-418-3898 were considered sufficient by the CHMP to determine the dosing regimen. See below.

Main study

The Cohort A Induction Study included biologic-naive subjects and the Cohort B Induction Study included biologic-experienced subjects. Both induction studies had a duration of 11 weeks and subjects were randomized in a 2:2:1 ratio to receive filgotinib 200 mg, filgotinib 100 mg, or placebo.

Subjects who completed the induction studies and achieved either endoscopy/bleeding/stool frequency (EBS) remission or Mayo Clinic Score (MCS) response at Week 10 were rerandomized into the Maintenance Study (Week 11 to Week 58). Subjects who received filgotinib in the induction phase were rerandomized in a 2:1 ratio to either continue on their initially randomised filgotinib dose or switch to placebo and subjects who received placebo in the induction studies continued on placebo in the maintenance phase.

Patient who did not meet the prespecified criteria for continuation into the maintenance phase, or who met disease-worsening criteria in the Maintenance Study, were discontinued from blinded treatment and had the option to receive open-label filgotinib 200 mg in Study GS-US-418-3899.

The inclusion and exclusion criteria clearly define patients with moderately to severely active UC (Mayo Clinic Score 6 to 12; endoscopy subscore ≥ 2; rectal bleeding subscore ≥ 1; stool frequency subscore ≥ 1; and Physician's Global Assessment subscore ≥ 2). Patients were permitted to use stable doses of concomitant therapies for UC, including oral aminosalicylates, oral corticosteroids (prednisone equivalent dose up to 30 mg/day), and immunomodulators (azathioprine, 6-MP, or methotrexate). In the Cohort A study, patients had to previously demonstrated an inadequate clinical response, loss of response to, or intolerance to at least one of the following agents: corticosteroids, oral azathioprine, 6-MP or MTX. In Cohort B study, patient had to previously demonstrated an inadequate clinical response, loss of response to, or intolerance to at least one TNF-α antagonist or vedolizumab.

The CHMP considered that the suggested indication text "*Jyseleca is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent*" adequately reflects the intended population.

As primary endpoint, the current study uses Endoscopic/Blood/Stool (EBS) remission, a combined endpoint derived from the Mayo clinical score (MCS), excluding the PGA. To reach EBS remission, the patient requires to have achieved an endoscopic response (a subscore of 0-1), cessation of rectal bleeding (subscore 0) and at least a 1-point decrease in stool frequency from baseline to achieve a subscore of 0 or 1. Although not fully consistent with the recommendations of the applicable guideline CHMP/EWP/18463/2006 rev 1 (stating that the endoscopic and clinical remission should be evaluated as co-primary endpoints) the above definition of remission is deemed acceptable by the CHMP because it did encompass both symptomatic and endoscopic remission and the sub-scoring levels chosen are consistent with the guideline, which states that a score of 0 or 1 may be used for defining endoscopic healing and symptomatic remission should include cessation of rectal bleeding. Some more stringent definition could have been used, such as endoscopic remission, but this is included as secondary outcome. The study also started before the publication of the updated EMA guideline. However, since the EMA guideline states that clinical (symptoms) and endoscopic remission should be evaluated as co-primary endpoints, additional analysis was requested to further evaluate the contributions of the different parts of the composite EBS-remission endpoint to the overall results (see below).

In addition, the study has several key secondary endpoints, based on different parts of the MCS and also histologic remission which is appreciated. Quality of Life and biomarkers are exploratory endpoints. The CHMP/EWP/18463/2006 guideline requires that for a claim of "maintenance of remission", it needs to be demonstrated that patients being in complete remission at study entry remain in remission throughout a full 52-week study period. As the maintenance study included both responders and remitters after induction, the most relevant endpoints for this assessment are therefore the key secondary endpoints sustained remission and corticosteroid-free clinical remission.

Globally, the objectives and endpoints of the SELECTION study are acceptable; however, the MAH was requested by the CHMP to further justify the histologic remission endpoint and to provide its definition. The MAH clarified that they referred to the recent ECCO position paper on the Harmonization of the Approach to Ulcerative Colitis Histopathology (Magro 2020). The definition of histologic remission in study GS-US-418-3898 incorporated a mild increase of inflammation, absence of neutrophils/erosion/ulceration and absence of crypt destruction. It is therefore broadly consistent with the ECCO position paper and was considered acceptable by the CHMP.

The secondary endpoints time to remission and time to response recommended in EMA guideline CHMP/EWP/18463/2006 was not included in the study outcomes. However, the MAH referred to the analyses first presented in the final report of the clinical study GS-US641863898 (SELECTION). They describe changes from baseline in the stool frequency and rectal bleeding sub scores of the primary endpoint MCS through week 10 of the induction studies, and changes from baseline in serum CRP and fecal calprotectin levels through week 10 of the induction studies.

The study was conducted at 341 study centres in 40 countries. Study Start Date was 14 November 2016 and study End Date 31 March 2020.

In Cohort A induction study (biologic naïve subjects) 1090 subjects were screened, and 660 subjects were randomized (245 patients received 200mg filgotinib, 277 patients received 100mg filgotinib and 137 patients received placebo). Overall, 630 subjects (94.8%) completed study drug dosing through week 10 and 618 subjects (93.8%) completed the cohort A introduction study. The main reasons for study drug discontinuation were subject decision and AEs, with a similar distribution between randomized groups.

In Cohort B induction study (biologic experienced subjects) 950 subjects were screened, and 691 subjects were randomized (262 patients received 200mg filgotinib, 285 patients received 100mg filgotinib and 143 patients received placebo). Overall, 623 subjects (90.4%) completed the cohort B introduction study. The main reasons for study drug discontinuation were AEs and subject's decision.

Of the 1241 subjects who completed the induction studies, 664 subjects continued to the maintenance study (53.5%). The 571 subjects treated with filgotinib in the induction phase were rerandomized in a 2:1 ratio to either continue on the assigned filgotinib regimen or switch to placebo. The 93 subjects who were treated with placebo in the induction phase continued with placebo treatment also during the maintenance phase. A total of 401 patients (60.4%) completed the maintenance phase, numerically more in the filgotinib/filgotinib 200 mg group (150/202, 74.3%) than in the filgotinib/filgotinib 100 mg group (104/179, 58.1%) and the placebo groups (filgotinib 200mg/placebo 41/99, 41.4%, filgotinib 100mg/placebo 42/91 46.2% and placebo/placebo group 64/93, 68.8%). The main reason for discontinuation were disease worsening (filgotinib 200mg: 34 subjects, 16.8%; respective placebo: 49 subjects, 49.5%; filgotinib 100mg: 53 subjects, 29.6%; respective placebo: 39subjects, 42.9%)

In the Cohort A induction study, the mean (SD) age of subjects was 42 (13.1) years. Fewer than half of subjects were female (44.3%) and most subjects were white (68.6%) or Asian (29.4%). Most subjects (90.0%) were from countries outside of the US. Demographics and other baseline characteristics were balanced across treatment groups except for slightly more woman in the placebo group that does not have any impact on the overall result. The mean (SD) duration of UC from diagnosis to first dose of study drugs was 6.8 (7.20) years. Mean (SD) MCS at baseline was 8.6 (1.36), and 52.4% of subjects had an MCS ≥ 9. In total, 55.8% of subjects had an endoscopic subscore of 3 at baseline. Thus, the study population comprises of patients with an active moderate to severe disease which are in line with the proposed indication.

With respect to concomitant immunosuppressant use, the proportions of subjects taking immunomodulators at baseline were 29.7% (only immunomodulators 22.6% and in combination with systemic corticosteroids 7.1%). 23.5% had systemic corticosteroids only. The proportion of subjects with concomitant use of systemic corticosteroids or immunomodulators at baseline was evenly distributed across treatment groups.

In the Cohort B Induction study, the mean (SD) age of subjects was 43 (14.4) and 39% were female. Demographics and other baseline characteristics were balanced across treatment groups in both cohorts.

The mean (SD) duration of UC from diagnosis to first dose of study drugs was 9.8 (7.56) years. Mean (SD) MCS at baseline was 9.3 (1.35), and 73.7% of subjects had an MCS ≥ 9. In total, 77.8% of subjects had an endoscopic subscore of 3 at baseline. It is not unexpected that this cohort, consisting of biologic experienced patients, have a higher disease activity and longer disease duration than biologic naïve patients. Prior use and prior failure of a TNF-α antagonist was reported for 92.6% and 85.5% of subjects. Prior use and prior failure of vedolizumab was reported for 57.2% and 51.7% of subjects. Prior use of both a TNF-α antagonist and vedolizumab was reported for 50.9% of subjects and prior failure of both a TNF-α antagonist and vedolizumab was reported for 43.1% of subjects.

The use of at least 3 biologic agents was reported in 30.9% of subjects.

With respect to concomitant immunosuppressant use, the proportions of subjects taking immunomodulators was 22.6% (only immunomodulators 12.9% or in combination with systemic corticosteroids 9.7%). 36.0 % were taking only systemic corticosteroids and 41.4% of subjects were taking neither systemic corticosteroids nor immunomodulators. The proportions of subjects with concomitant use of systemic corticosteroids or immunomodulators at baseline and the proportions of subjects previously exposed to 1 biologic agent or >1 biologic agent at baseline were evenly distributed across treatment groups.

Thus, the cohort B consist of a population with a high disease activity despite previous use of biologics. Almost a third of the patients (30.9%) had used at least 3 biologics and half of the patients (50.9%) had used both a TNF inhibitor and vedolizumab.

Statistical aspects study GS-US-418-3898

In the induction studies, an interim analysis for futility was planned and seemingly also performed after 175 subjects had completed week 10 assessments or discontinued from the study. At the time, the data monitoring committee (DMC) could have recommend terminating a filgotinib dose group or recommended stopping the study if the observed proportion of subjects who had achieved endoscopic response in one or both filgotinib dose groups was less than that in the placebo group; the study did however complete according to plan. An unblinded interim End-of-Induction Analysis for a prespecified sponsor's executive team review for the purpose of sponsor decision making and future development planning for filgotinib was first added but shortly after removed (protocol amendment 5.0 and 5.1 respectively). The removal was considered acceptable to the CHMP.

There are no concerns regarding randomisation or masking of treatments. With filgotinib available as 200 mg and 100 mg strength tablets, blinding was to be achieved using double-dummy technique and should have been appropriate. The sample size estimations seem overall to have been appropriate. The actual sample size in the maintenance study depended on the outcome in the induction cohorts. An induction response rate of 55% was assumed among filgotinib treated subjects and thereby that approximately 285 subjects from each filgotinib dose group from cohorts A and B combined could be eligible for re-randomisation into the maintenance study. In the end, 297 from the 200 mg filgotinib dose group and 261 from the 100 mg filgotinib dose group were re-randomised and included in the primary analysis set. Subjects who received placebo in the induction studies and were eligible for the Maintenance Study continued on placebo; they were not included in the primary analysis of the maintenance study.

SAP version 3.0 was dated 28 April 2020, i.e. close to but before database finalisation and treatment unblinding (5 and 6 May 2020). Planned analyses are overall agreed. Previous SAP versions have been submitted including a section describing SAP revisions. Overall, no concerns are raised; changes made foremost concerned clarifications or modifications not considered to have any major impact on primary conclusions. The multiple testing procedure was initially planned to use Bonferroni alone but was updated to allow alpha recycling between the two testing sequences for the two filgotinib doses. This

update concerned both the two induction cohorts and the maintenance study and is agreed. To protect the integrity of the study due to the unblinded interim futility analysis planned for each induction study, an alpha adjustment of 0.00001 was used for each filgotinib dose group comparison to placebo implying that comparisons (within each induction study) was performed using a two-sided significance level of 0.02499. While an alpha spending approach is generally not expected in terms of futility analyses, there is no objection against.

The most important endpoints were all binary and used a failure imputation approach. Within the induction cohorts, most subjects completed study drug dosing through week 10. Several sensitivity analyses for the primary endpoint was planned and have been performed (both induction cohorts and the maintenance study). These are overall appreciated in that they represent a number of assumptions, including the more (most) extreme worst case (filgotinib)/best case (placebo) imputation. Overall, most subjects completed the induction studies; more subjects did however discontinue in the placebo arms compared with subjects in the active arms and more subjects discontinued in the 100 mg arm compared with the 200 mg arm.

The multiple testing procedures comprised, besides the primary endpoint, a number of key secondary endpoints. The multiplicity testing procedure set in the trial is endorsed within each phase of the trial (induction and maintenance). The reasons for no type-one error control between the induction and maintenance stage were not discussed; however, this issue has not been further pursued by the CHMP since this would not impact the final decision.

The change-from-baseline analyses of HRQoL endpoints used LOCF. This is not a preferred choice of method to handle cases where data was missing. For the maintenance study, sensitivity analyses were provided and performed using BOCF; assuming no treatment effect and hence that subjects maintained their baseline HRQoL status as when they were randomised. Since subjects at randomisation had to be responders this approach is sufficiently conservative because of more subjects with missing week 58 data in the placebo arm than in active arms. The omittance of sensitivity analyses for the induction studies was accepted by the CHMP. Here, the amount of missing data was more limited and the use of LOCF actually implied BOCF due to that there was only one post-baseline measurement.

Maintenance study only

In the Maintenance study compared with induction studies, there were many more subjects that prematurely discontinued study drug/the study. Most of them, both in the placebo as well as in the 200 mg arm, did so due to a protocol-specified disease worsening. Given the nonetheless much higher proportion of subjects in the placebo arm fulfilling this criterion during maintenance, a difference between 200 mg and placebo was evident also in the worst case/best case sensitivity analysis. The criteria of disease worsening have been found acceptable.

Long-term extension study GS-US-418-3899

Subjects who completed the Week 58 visit in the Maintenance Study had the option to continue study drug in a blinded fashion in the long-term extension study which is still ongoing. Treatment assignments for subjects continuing in study GS-US-418-3899 was unblinded only after study GS-US-418-3898 was unblinded. At the time of unblinding, subjects who were receiving placebo in GS-US-418-3899 were discontinued and subjects who were receiving filgotinib treatment continued on the same dose of open-label filgotinib treatment.

Efficacy data and additional analyses

Dose selection

The overall data from the Phase 2 Study in patients with Crohn's disease (GLPG0634-CL-211) are limited and no relevant conclusion can be drawn from the Exposure-response relationships evaluated based on data from the phase 2b/3 study (GS-US-418-3898) in patients with UC. However, based on the efficacy and safety results of the pivotal phase 2b/3 study GS-US-418-3898, the CHMP agreed that the 200mg dose once daily regimen was appropriate in the claimed indication.

Main study

In the **biologic naïve patients** (Cohort A study), the primary endpoint, EBS remission at week 10, was achieved by 26.1% in the filgotinib 200 mg group, 19.1% in the filgotinib 100 mg group and 15.3% in the placebo group. Only the higher dose, filgotinib 200mg, was statistical significantly better than placebo (difference in proportions were 10.8% (95% CI: 2.1% to 19.5%, p = 0.0157). The results from all the key secondary endpoints were in line with the results from the primary endpoint. It is noted that although only 12.2% achieved endoscopic remission (i.e. mayo endoscopic score 0), 33.9% achieved endoscopic response (score 0-1), an outcome that often are defined as mucosal healing (exploratory endpoint and also the endoscopic part of the EBS-score). In the placebo group the proportion were 3.6% for endoscopic remission and 20.4% for endoscopic response. Histologic remission was seen in 35% of patients in filgotinib 200mg group and 16% in the placebo group (difference in proportions were 19% (95% CI 9.9% to 28.2%, P<0.0001). At the CHMP's request, the MAH was asked to clarify why histologic remission is achieved at a later timepoint than both clinical and endoscopic remission. The MAH pointed out that the poor correlation between histologic findings and clinical or endoscopic indices of activity for UC are historically known. In particular, the recent article by Lemmens notes that endoscopic and histologic changes should be seen as 2 dynamic processes not necessarily running completely in parallel. This was considered acceptable to the CHMP.

In addition, all exploratory endpoints showed numerically greater efficacy for filgotinib 200 mg than placebo. Of note, the patients who achieved a MCS response at week 10 were allowed to proceed to the maintenance study. The proportions of patients achieving a MCS response were 66.5% (163/245) in the filgotinib 200 mg group, 59.2% (164/277) in the filgotinib 100 mg group and 46.7 (64/137) in the placebo group. Although numerically more patients in the filgotinib groups, especially filgotinib 200 mg, achieved a MCS response at week 10, it is noted that not an insignificant proportion of patients in the placebo group achieved MCS response at week 10 and were allowed to proceed into the maintenance study.

There were numerical differences in favour for filgotinib in several parts of the patient reported outcomes related to Quality of life and upon CHMP request, the MAH provided additional information regarding the number and proportion of patients achieving minimal clinical important difference (MCID) in these endpoints. Minimal clinically important difference was defined as an increase from induction baseline of the following: ≥ 16 in the IBDQ total score, ≥ 5 in the respective SF-36 physical component summary or mental component summary, and ≥ 10 in the EQ-5D-VAS, and a decrease of ≥ 7% from induction baseline in each WPAI domain score. The proportion of patients achieving a MCID were in general higher in the filgotinib group versus the placebo group with the exception of WPAI, where the proportion of patients achieving a MCID in absenteeism, presenteeism and work productivity loss were similar in the filgotinib and the placebo group.

In the **biologic experienced patients** (Cohort B study), EBS remission at week 10 was achieved by 11.5% in the filgotinib 200 mg group, 9.5% in the filgotinib 100 mg group and 4.2% in the placebo

group. Also, in this cohort, only the higher dose, filgotinib 200mg, was statistical significantly better than placebo (difference in proportion was 7.2% (CI 1.6% to 12.8%, p=0.013). None of the key secondary endpoints were statistically significant in this patient group, although it is noted that for histologic remission there was a numerically increase in favour for filgotinib 200 mg 19.8% vs 8.5%. Only 3.4% and 17.2% patients achieved endoscopic remission and endoscopic response. Although this patient group consisted of patients with a more severe disease, resistant to biologic therapies (50% of the patients had received both a TNF-inhibitor and vedolizumab), the clinical relevance of the modest efficacy seen in this patient group was questioned by the CHMP. In particular, there was a concern that the endpoint considered to be predictive for the long-term outcome/prognosis of the patients (endoscopic improvement/remission) was not achieved at a relevantly higher rate with filgotinib as compared to placebo. The MAH clarified these findings and provided additional information. When clinical and endoscopic response were analysed separately, it was obvious that the main efficacy result achieved from the endpoint EBS-remission was mainly based on the symptomatic response (36.3% vs 10.6%, difference in proportions 26.6 (18.6 to 34.6)). However, a numerically better response could be seen also in the endoscopic part of the EBS-remission endpoint, 17.2% vs 7.7% difference in proportions 9.4 (2.5 to 16.7). The additional information provided by the MAH regarding mucosal healing (defined as endoscopic response in combination with histological remission), showing that a numerically greater proportion of biologic-experienced subjects achieved mucosal healing in the filgotinib 200 mg group compared with the placebo group both at week 10 (9.9% versus 4.2%, difference in proportion 6.0 (0.4 to 11.7)) and at Week 58 (22.8% vs 4.5%, difference in proportion 18.3 (6.0 to 30.0)), added further evidence that a beneficial effect is seen also on the mucosa. It may be expected that this patient group could achieve clinical remission at a later timepoint, and it is noted that more than half of the patients in the filgotinib 200 mg group (53.1%) achieved MCS response at week 10. In the filgotinib 100 mg and placebo group, 35.8% respectively 17.6% achieved MCS response at week 10. These patients were allowed to proceed to the maintenance study.

It is acknowledged that the cohort B study population included a significant proportion of patients who were very treatment resistant to biologic agents. It can also be agreed that, among the populations in registrational UC trials to date, it was the most refractory with a substantial prior treatment history of biologic therapies and a high disease burden at baseline. Results of the subgroup analysis by history of biologic agent use show that the treatment effect of filgotinib 200mg is reduced in refractory patients, in particular patients with prior failure to vedolizumab and dual refractory patients (with prior failure of both TNF-α antagonist and vedolizumab). Upon request from CHMP, results of the subgroup analysis of EBS remission endpoint by history of biologic agent use were included in SmPC section 5.1 to adequately inform the prescriber on this issue.

The findings from the two induction studies support the suggested posology 200mg for both biologic naïve and experienced patients in the induction phase.

The CHMP recognized that the variability of the data is high. Although a clear conclusion on the time to remission and time to response has not been established, declines in symptom scores and biomarkers are found to occur as early as week 2, reflecting a fairly rapid effect of filgotinib.

To substantiate the contributions of clinical and endoscopic parts to the total EBS-score, the MAH was asked to evaluate the numbers and proportions of patients in clinical remission (i.e. patients with at least a 1-point decrease in stool frequency from baseline to achieve a subscore of 0 or 1 and a rectal bleeding score 0) and numbers and proportions of patients in endoscopic response (i.e. mayo endoscopic score 0-1) separately and discuss the findings in relation to the total EBS-remission endpoint. The data provided showed that for both the symptomatic remission and endoscopic response, a numerical clinically relevant efficacy was seen. Also, when analysing the two components

of the symptomatic remission part (rectal bleeding and stool frequency) a numerical difference in favour for filgotinib 200 mg was seen.

Overall, although the main efficacy was seen on the symptoms in the biologic experienced patients, a modest efficacy was also seen when evaluating the response on the mucosa. Since the biologic experienced patients population included a rather high proportion of dual-refractory patients, those data are reflected in Section 5.1 of the SmPC.

In the **maintenance study**, statistically significant treatment differences between filgotinib 200 mg and placebo at Week 58 were observed for the primary and all key secondary endpoints. The primary endpoint, EBS remission at week 58, was reached by 37.2% of the Filgotinib 200 mg group and 11.2% of the placebo group. Difference in proportion was 26.0% (95% CI 16.0% to 35.9%, p< 0.0001).

The proportions of subjects who achieved 6-month corticosteroid-free EBS remission at Week 58 were 27.2% in the 200 mg group respective 6.4 % in the placebo group (difference in proportion 20.8% CI 7.7% to 33.9%). Upon CHMP request, the MAH also provided information regarding numbers and proportions of patients in corticosteroid free symptomatic remission at week 58 (42.2% vs 19.1% difference in proportions 23.2 (6.5 to 40.0) and with corticosteroid-free endoscopic response at week 58 (29.3% vs 8.5%, difference in proportions 20.8 (7.0 to 34.7)). This additional analysis consistently shows numerical superiority of filgotinib 200 mg over placebo for all endpoints in both biologic-naïve and biologic experienced patients. The magnitudes of effects were smaller in the biologic experienced patients, but this is generally expected and the "corticosteroid free" remission at week 58 in biologic experienced patients is mainly driven by clinical symptoms, not by mucosal healing. Indeed, with regard to the proportion of patients with 6-month corticosteroid-free endoscopic response, the magnitude of effect is only 6.3% (14.3% (7/49)) versus 8.0% ((2/25), 95%CI= -11.2% to 23.8%), it is much larger for the proportion of patients with 6-month corticosteroid-free symptomatic response (30.6% (15/49)) versus (12.0% (3/25), difference = 18.6%, 95%CI = -2.5% to 39.8%). Bearing in mind that this bio-experienced population was particularly refractory to treatment, the "corticosteroid-free" benefit observed on the long term in this population can be considered clinically relevant, though it is mostly driven by symptoms and to a lesser extent by mucosal healing.

There were some discrepancies between the number of patients reported to be on corticosteroid treatment at the beginning of the maintenance phase and the number of patients included in the analyse of the corticosteroid treated patient, and this discrepancies were due to different definition of corticosteroid treatment and did not have any impact on the results. In addition, since numerically more patients in the placebo group received a corticosteroid dose >20mg (18.2% in the placebo group vs 8.4% in the 200 mg group) the MAH provided additional analyses that confirmed that this discrepancy did not had any effect on the result. Since patients were considered treatment failures if the corticosteroid dose were increased above initial treatment dose, but not otherwise, additional information about corticosteroid treated patients were provided by the MAH upon request. Of the 92 subjects in the maintenance filgotinib 200 mg group who had corticosteroid use at maintenance baseline, the majority (58 subjects, 63.0%) had stopped corticosteroid treatment, few subjects had not changed (3 subjects, 3.3%) or had reduced (5 subjects, 5.4%) their corticosteroid dose, and no subject had increased their corticosteroid dose at Week 58. In the respective placebo group, 14 subjects (29.8%) had stopped corticosteroid treatment, no subject had reduced their corticosteroid dose, and few subjects had increased their corticosteroid dose (1 subject, 2.1%) or had not changed their corticosteroid dose (2 subjects, 4.3%) at Week 58. The number of subjects who met the treatment failure rule in the Maintenance Study was small, with no apparent discrepancy across treatment groups.

Although statistically significant different from placebo, the proportion of subjects who achieved sustained EBS remission at Week 58 seems low, only 18.1% in the Filgotinib 200 mg group and 5.1%

in the respectively placebo group. Upon CHMP request, the MAH provided additional tabulations confirming that of the subjects with EBS remission at Week 10 who received filgotinib 200 mg during induction and maintenance, 62.1% achieved EBS remission at Week 58.

In addition, to further explore the benefit of long term/maintenance treatment, the MAH provided additional information regarding the patients who achieved MCS-response (but not remission) at week 10. In that population, 38/141 (27.0%) vs 6/67 (9.7%) and 39/146 (26.7%) vs 4/66 (6.1%) achieved EBS- and MCS-remission, respectively, at week 58, thus indicating that additional efficacy could be gained for this patient group. In addition, since it is noted that 64/93 (68.8%) of the patients that were placebo-responders at week 10 completed the maintenance phase, the MAH provided additional information about efficacy also in this population. In the placebo responder group, of the subjects who achieved MCS-response (but not remission) at week 10 and continued to the maintenance phase still on placebo, 7/61 (11.5%) achieved EBS remission at Week 58 and 8/65 (12.3%) achieved MCS remission at Week 58.

Treatment differences between filgotinib 100mg and respective placebo group were statistically significant for the primary endpoint (Filgotinib 100 mg: 23.8%, respective placebo: 13.5%; difference in proportions: 10.4%, 95% CI: −0.0% to 20.7%, p = 0.0420), but not for any of the key secondary endpoints at Week 58. In addition, 29.6% of the patients in the 100mg group discontinued the medication because of disease worsening. This does not support the use of the lower dose for maintaining treatment in the overall UC population, but the CHMP noted that the study did not analyse the effect of a higher induction dose followed by a lower maintenance dose. Since the clinical course in UC usually involves periods of remission interspersed with periods of active disease, the treatment approach in UC aims to induce a fast remission followed by maintenance treatment if the patient responds. Thus, at the CHMP's request, the MAH proposed the following points which were considered acceptable by the CHMP:

- Section 4.2 of the SmPC was updated based on data from the long-term evaluation study to suggests 12 additional week of treatment after the initial 10 weeks before discontinuing the treatment if no effect is seen.
- The MAH will conduct a study exploring a reduction of maintenance dose in a post-marketing setting. The proposed study would recruit subjects from the ongoing long term extension (LTE) study (GS US 418 3899 [SELECTION LTE]) who are in stable glucocorticosteroid free partial MCS remission while receiving filgotinib 200 mg daily. These patients would be randomized to either 200 mg or 100 mg daily.

Since the maintenance study was randomized withdrawal study, it is not unsuspected to the CHMP that more than 50% of the patients re-randomized from filgotinib to placebo discontinued study drug (58.6% in the filgotinib 200 mg/placebo group and 53.8% in the filgotinib 100 mg/placebo group, 41.9% in the filgotinib 100 mg group and 25.7% in the filgotinib 200 mg group). As described previously, the main reason for discontinuation was disease worsening.

Subgroup analyses indicate efficacy in both bio-naïve and bio experienced patients in the maintenance study. The proportion of bio-experienced patients achieving EBS remission at week 58 was 22/92(23.9%) and the proportion of bio-naïve patients was 52/107 (48.6%). To further explore efficacy in this subgroup, the MAH provided the other key secondary endpoints divided in the two groups. For the bio-naïve patients, the results were in line with the results achieved in the whole population. For the bio-experienced population a numerically greater proportion of biologic-experienced subjects in the filgotinib 200 mg group achieved a response in the key secondary endpoints, although it is noted that for several endpoints the lower bound of CI were close to zero or below. However, the CHMP noted that the study was not designed to detect any difference in

subgroups. In general, the point estimate points toward a beneficial effect for filgotinib 200 mg also in the bio-experienced population at week 58.

In addition, the treatment effect of filgotinib 200 mg compared with placebo in establishing EBS remission at Week 58 was consistent across all subgroups by stratification, demographic factors, disease characteristics, and prior biologic history. A numerically higher proportion of patients achieved EBS remission at week 58 compared to placebo in the subgroups of patients with prior failure to TNF-α antagonists (22.7% vs 5.3%, difference 17.4%), and prior failure to vedolizumab (27.5% vs 0%), and dual refractory (25.8% vs 0%). In order to verify the consistency in establishing sustained EBS remission at week 58 and 6-month corticosteroid-free EBS remission at Week 58, the MAH has also provided subgroup analyses of sustained EBS remission at week 58 and 6-month corticosteroid-free EBS remission at Week 58 by concomitant use of systemic corticosteroids, immunomodulators at baseline. The CHMP concluded that the treatment effect of filgotinib 200 mg is consistent also across these subgroups.

Long-term extension study GS-US-418-3899

An interim analysis of the results from the long-term extension study GS-US-418-3899 was provided (DLP=05 May 2020, safety analysis set n= 1161, 144 weeks follow-up). The results showed that continued treatment with filgotinib 200 mg provided some symptomatic clinical benefit, as evidenced by the downward trend in partial MCS from baseline starting at week 2. The improvement in MCS appeared to be sustained up to 108 weeks. After that, the number of patients was too small to draw conclusions. In addition, HRQoL evaluations showed trends of improvement. The mean change from baseline in partial MCS was greater with filgotinib 200 mg than with filgotinib 100 mg.

Although the focus of the long-term extension study is safety, some information about efficacy could be achieved also from this study and to further explore the overall benefit of the treatment the MAH was asked to provide additional information about the patients that were non responders at week 10 and continued into the long-term study GS-US-418-3899. The result showed that patients from Cohort A and Cohort B achieved partial MCS remission (17.1% and 16.7%, respectively) and partial MCS response (65.7% and 62.2%, respectively) after 12 weeks of additional treatment in the LTE study. This information has been included in SmPC section 5.1.

2.4.4. Conclusions on the clinical efficacy

A statistically significant and clinically relevant effect as measured by EBS remission has been demonstrated for Jyseleca 200 mg QD, both as induction and maintenance treatment, in the target population of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

For patients with previous biological therapy, the treatment effect was modest, and none of the secondary endpoints in the induction phase reached statistically significance. This patient group consisted of patients with a more severe disease, resistant to biologic therapies, and a lower efficacy in this population is thus acceptable.

Overall, there is support from secondary endpoints measuring different aspects of the disease.

Finally, the study did not evaluate the effect of a higher induction dose followed by a lower maintenance dose and, at the CHMP's request, the MAH accepted to conduct a study exploring a reduction of maintenance dose in a post-marketing setting.

In conclusion, the CHMP considered that the data submitted supports the claimed indication and the dosing recommendations.

2.5. Clinical safety

Introduction

Table 47 Overview of the Integrated Safety Analyses for the Ulcerative Colitis Development Program

Safety Analysis Cohort	Study Period	Treatment Duration	Treatment Regimens	Subject Population (Safety Analysis Set)
Cohort 1	Cohort A and Cohort B Induction Studies combined from Study GS-US-418-3898	Up to 11 weeks	Filgotinib 200 mg QD, filgotinib 100 mg QD[a], or placebo QD (2:2:1 ratio)	Cohort A Induction Study: biologic-naive adult subjects with moderately to severely active UC (N = 659) Cohort B Induction Study: biologic-experienced adult subjects with moderately to severely active UC (N = 689)
Cohort 2	Maintenance Study from Study GS-US-418-3898	Up to 47 weeks	Filgotinib 200 mg QD and respective placebo; filgotinib 100 mg QD[a] and respective placebo (2:1 filgotinib to placebo), or placebo QD	Subjects who achieved EBS remission or MCS response at Week 10 in the induction studies (N = 664)
Cohort 3	Studies GS-US-418-3898 and GS-US-418-3899 combined	Entire safety experience in the UC development program	Filgotinib 200 mg QD, filgotinib 100 mg QD, or placebo QD[b]	Biologic-naive and biologic-experienced subjects with moderately to severely active UC from Studies GS-US-418-3898 and GS-US-418-3899 (N = 1348)

EBS = endoscopy/bleeding/stool frequency; MCS = Mayo Clinic Score; QD = once daily; UC = ulcerative colitis

a US and Korea males who were not dual refractory (having failed any TNF-α antagonist and vedolizumab) were randomized 2:1 to either filgotinib 100 mg or placebo.

b For Cohort 3, safety events that occurred while on a given treatment were assigned to that corresponding treatment.

Adverse events, laboratory abnormalities, and marked laboratory abnormalities were reported for events that occurred within a study or treatment period and up to 30 days after the last dosing date within the same study or treatment period. Long-latency AEs included AEs that occurred after the last dosing date + 30-day follow-up and before the first dosing date of the next study, if applicable.

The exposure-adjusted integrated safety analysis is based on the Safety Analysis Set, which comprises all subjects enrolled in Studies GS-US-418-3898 or GS-US-418-3899 who received at least 1 dose of study drug. By-subject listings of safety data are based on the All Randomized Analysis Set, which includes all subjects who were randomized into Cohort A Induction Study or Cohort B Induction Study of Study GS-US-418-3898.

For analyses based on the Safety Analysis Set for Cohort 1, data were grouped according to the treatment received in the induction studies: filgotinib 200 mg, filgotinib 100 mg, or placebo.

For analyses based on the Safety Analysis Set for Cohort 2, data were grouped according to the treatment received in both induction and maintenance studies as follows: filgotinib 200 mg and its respective placebo; filgotinib 100 mg and its respective placebo; and placebo only.

For analyses based on the Safety Analysis Set for Cohort 3, safety events that occurred while on a given treatment were assigned to that corresponding treatment. Safety events that occurred after the last dosing date across the induction, maintenance, and LTE studies were assigned to the last treatment period for the subject. Based on the study designs of Studies GS-US-418-3898 and GS-US-418-3899, subjects may have received different treatments (filgotinib 200 mg, filgotinib 100 mg, or placebo) in the induction, maintenance, and LTE studies. Accordingly, subjects may have contributed to more than 1 treatment group.

Treatment period was defined as a treatment duration for each treatment a subject received. For Cohort 3, whenever there was a switch in treatment regimen, the data collected after the treatment switch were assigned to the next treatment period. For example, if a subject received the same treatment, such as filgotinib 200 mg throughout Studies GS-US-418-3898 and GS-US-418-3899, the subject was considered to have had only 1 treatment period. A subject who received filgotinib 200 mg during induction treatment, placebo in the Maintenance Study, and filgotinib 200 mg in Study GS-US-418-3899 was considered to have had 3 treatment periods.

Patient exposure

In Cohort 1 (combined cohort A and cohort B induction study), overall, 1069 subjects received at least 1 dose of filgotinib for a total of 221.1 PY, comprising 507 subjects treated with filgotinib 200 mg for 105.2 PY and 562 subjects treated with filgotinib 100 mg for 115.8 PY. A total of 279 subjects received placebo for 57.0 PY.

For Cohort 2 (maintenance study), overall, 381 subjects received at least 1 dose of filgotinib for a total of 270.7 PY, comprising 202 subjects treated with filgotinib 200 mg for 152.4 PY and 179 subjects treated with filgotinib 100 mg for 118.3 PY. A total of 99 subjects and 91 subjects were treated with the respective placebos for filgotinib 200 mg and filgotinib 100 mg for 54.6 PY and 50.9 PY, respectively.

Overall, a total of 1253 subjects with UC have received at least 1 dose of filgotinib for a total of 1567.4 PY (table below).

Table 48. Duration of Exposure to Filgotinib Among Subjects in Cohort 3 (GS-US-418-3898 and GS-US-418-3899 Combined; Safety Analysis Set)

	Filgotinib 200 mg	Filgotinib 100 mg	Filgotinib Total	Placebo
N	971	583	1253	469
Total PY	1207.4	360.0	1567.4	318.0
Total Treatment Duration (Weeks)				
N	971	583	1253	469
Mean (SD)	64.9 (37.14)	32.2 (35.44)	65.3 (39.17)	35.4 (35.72)
Median	67.1	11.4	68.1	12.0
Q1, Q3	33.7, 93.6	11.0, 50.6	28.0, 96.3	10.9, 59.9
Min, Max	0.4, 166.7	0.3, 163.4	0.3, 166.7	0.9, 131.6
Cumulative N (%) of Subjects with Treatment Duration				
≥ 1 Day	971 (100.0%)	583 (100.0%)	1253 (100.0%)	469 (100.0%)
≥ 30 Days	943 (97.1%)	563 (96.6%)	1213 (96.8%)	441 (94.0%)
≥ 90 Days	832 (85.7%)	234 (40.1%)	1040 (83.0%)	229 (48.8%)
≥ 180 Days	763 (78.6%)	180 (30.9%)	951 (75.9%)	181 (38.6%)
≥ 365 Days	621 (64.0%)	141 (24.2%)	800 (63.8%)	130 (27.7%)
≥ 730 Days	158 (16.3%)	39 (6.7%)	232 (18.5%)	34 (7.2%)
≥ 1095 Days	3 (0.3%)	1 (0.2%)	4 (0.3%)	0

Min = minimum; Max = maximum; PY = person-years ([last dosing date - first dosing date + 1]/365.25 per subject); Q1 = first quartile; Q3 = third quartile; SD = standard deviation

Completely missing last study drug dose date was imputed to the latest date among the study drug end date and on-treatment clinical/laboratory visit dates. Partially missing last study drug dose date was imputed to the earliest date among the last date of that month and the last on-treatment clinical/laboratory visit date of that month; otherwise last dose date was imputed to the 15th of that month. If subjects were continuing study drug at the data cutoff date for an interim analysis, the data cutoff date was used to impute the last dosing date.

If a subject was on different treatments across different treatment periods, this subject was included into more than 1 treatment groups with treatment duration summarized under separate columns accordingly.

Adverse events

Overall summaries of EAIRs for the AEs reported in Cohort 1 (Cohort A Induction Study and Cohort B Induction Study Combined) and Cohort 2 (Maintenance Study) are provided in the tables below along with a summary of EAERs for AEs in Cohort 3.

Table 49. Overall Summary of Exposure-Adjusted Incidence Rates of Adverse Events Among Subjects in Cohort 1 (Cohort A Induction Study and Cohort B Induction Study Combined; Safety Analysis Set, treatment duration 11 weeks)

	Filgotinib 200 mg (N=507)	**Filgotinib 100 mg (N=562)**	**Placebo (N=279)**	**EAIR Difference (95% CI)**		
Subjects with Any	**n/PYE EAIR (95% CI)**	**n/PYE EAIR (95% CI)**	**n/PYE EAIR (95% CI)**	**Filgotinib 200 mg vs Placebo**	**Filgotinib 100 mg vs Placebo**	**Filgotinib 200 mg vs 100 mg**
TEAE	271/69.3	282/80.0	156/37.0			
	391.0 (345.8,440.4)	352.4 (312.5,396.0)	422.1 (358.5,493.8)	-31.1 (-115.8,49.5)	-69.7 (-151.8,7.4)	38.6 (-24.2,102.1)
TEAE with Grade 3 or Higher	35/104.7	47/115.4	31/55.4			
	33.4 (23.3,46.5)	40.7 (29.9,54.2)	56.0 (38.0,79.5)	-22.6 (-48.2,-0.4)	-15.3 (-41.1,7.1)	-7.3 (-24.1,9.6)
TE Serious AE	22/106.9	28/117.6	13/58.1			
	20.6 (12.9,31.2)	23.8 (15.8,34.4)	22.4 (11.9,38.3)	-1.8 (-19.4,13.1)	1.4 (-16.3,16.3)	-3.2 (-16.3,10.0)
TEAE Leading to Premature Discontinuation of Study Drug	22/106.8	19/118.5	14/58.0			
	20.6 (12.9,31.2)	16.0 (9.7,25.0)	24.2 (13.2,40.5)	-3.6 (-21.6,11.7)	-8.1 (-25.7,6.1)	4.6 (-7.3,16.9)
TE Serious AE Leading to Death	0	0	0			
Death	0	0	0			

AE = adverse event; EAIR = exposure-adjusted incidence rate per 100 PYE; PYE = patient-years of exposure; TE = treatment-emergent; TEAE = treatment-emergent adverse event

Treatment-emergent adverse events were defined as any AEs that began on or after the study first dose date and up to 30 days after the last dose date within the same study and prior to the first dose date of the next study, whichever was earlier.

Death included any death that occurred during the study.

Adverse events were coded according to Medical Dictionary for Regulatory Activities, Version 22.1. Severity grades were defined by the Common Terminology Criteria for Adverse Events, Version 4.03. Multiple AEs were counted only once per subject for the highest severity grade for each preferred term.

Exact Poisson distribution method was applied to compute the 95% CI of EAIR; the Method of Variance Estimates Recovery was used to compute the 95% CI of the difference between 2 EAIRs.

Table 50. Overall Summary of Exposure-Adjusted Incidence Rates of Adverse Events Among Subjects in Cohort 2 (Maintenance Study; Safety Analysis Set, treatment duration 47 weeks)

Subjects with Any	**Induction Filgotinib 200 mg**			**Induction Filgotinib 100 mg**			**Maintenance Filgotinib 200 mg vs 100 mg EAIR Diff (95% CI)**	**Induction Placebo**
	Maintenance Filgotinib 200 mg (N=202) n/PYE EAIR (95% CI)	**Maintenance Placebo (N=99) n/PYE EAIR (95% CI)**	**Maintenance Filgotinib 200 mg vs Placebo EAIR Diff (95% CI)**	**Maintenance Filgotinib 100 mg (N=179) n/PYE EAIR (95% CI)**	**Maintenance Placebo (N=91) n/PYE EAIR (95% CI)**	**Maintenance Filgotinib 100 mg vs Placebo EAIR Diff (95% CI)**		**Maintenance Placebo (N=93) n/PYE EAIR (95% CI)**
TEAE	134/80.1	57/31.4		107/72.7	60/30.3			57/40.6
	167.4	181.4	-14.0	147.2	198.3	-51.1	20.2	140.2
	(140.2,198.2)	(137.4,235.0)	(-74.1,39.8)	(120.7,177.9)	(151.3,255.3)	(-113.9,5.0)	(-20.8,60.9)	(106.2,181.7)
TEAE with Grade 3 or Higher	16/147.7	7/54.0		11/117.2	10/50.9			9/66.6
	10.8	13.0	-2.1	9.4	19.6	-10.3	1.5	13.5
	(6.2,17.6)	(5.2,26.7)	(-16.6,8.2)	(4.7,16.8)	(9.4,36.1)	(-27.4,2.4)	(-7.3,9.7)	(6.2,25.7)
	9/151.5	0/55.3		8/118.7	7/51.8			4/67.9
	5.9	0.0	5.9	6.7	13.5	-6.8	-0.8	5.9

TE Serious AE	(2.7,11.3)	(0.0,6.7)	(-1.5,11.3)	(2.9,13.3)	(5.4,27.8)	(-21.6,3.6)	(-8.1,5.8)	(1.6,15.1)
TEAE Leading to Premature Discontinuation of Study Drug	8/153.2	3/55.2		13/119.3	4/51.9			6/68.7
	5.2	5.4	-0.2	10.9	7.7	3.2	-5.7	8.7
	(2.3,10.3)	(1.1,15.9)	(-11.1,6.4)	(5.8,18.6)	(2.1,19.7)	(-9.9,12.7)	(-14.0,1.5)	(3.2,19.0)
TE Serious AE Leading to Death	2/154.0	0/55.3		0/120.4	0/52.3			0/69.0
	1.3	0.0	1.3	0.0	0.0	0.0	1.3	0.0
	(0.2,4.7)	(0.0,6.7)	(-5.5,4.7)	(0.0,3.1)	(0.0,7.1)	(-7.1,3.1)	(-2.0,4.7)	(0.0,5.3)
Death	2/154.0	0/55.3		0/120.4	0/52.3			0/69.0
	1.3	0.0	1.3	0.0	0.0	0.0	1.3	0.0
	(0.2,4.7)	(0.0,6.7)	(-5.5,4.7)	(0.0,3.1)	(0.0,7.1)	(-7.1,3.1)	(-2.0,4.7)	(0.0,5.3)

Table 51. Overall Summary of Exposure-Adjusted Event Rates of Adverse Events Among Subjects in Cohort 3 (GS-US-418-3898 and GS-US-418-3899 Combined; Safety Analysis Set)

	Non-model-based Descriptive Statistics			**Model-based EAER Ratio (95% CI)**		
Subjects with Any	**Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)**	**Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)**	**Placebo (N=469) (PYE=324.7) n (EAER*)**	**Filgotinib 200 mg vs Placebo**	**Filgotinib 100 mg vs Placebo**	**Filgotinib 200 mg vs 100 mg**
TEAE	3280 (265.8)	1182 (318.9)	1004 (309.2)	0.8 (0.7,0.9)	0.9 (0.7,1.0)	0.9 (0.8,1.0)
TEAE with Grade 3 or Higher	226 (18.3)	107 (28.9)	81 (24.9)	0.7 (0.5,0.9)	1.0 (0.7,1.6)	0.6 (0.5,0.9)
TE Serious AE	147 (11.9)	68 (18.3)	40 (12.3)	0.8 (0.5,1.3)	1.4 (0.8,2.5)	0.6 (0.4,0.9)

Subjects with Any	Non-model-based Descriptive Statistics			Model-based EAER Ratio (95% CI)		
	Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)	Placebo (N=469) (PYE=324.7) n (EAER*)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
TEAE Leading to Premature Discontinuation of Study Drug	171 (13.9)	69 (18.6)	43 (13.2)	0.9 (0.6,1.4)	1.3 (0.8,2.1)	0.7 (0.5,1.0)
TE Serious AE Leading to Death	4 (0.3)	0	0	NEst	NEst	NEst
Death	3 (0.2)	0	0	NEst	NEst	NEst

AE = adverse event; EAER = exposure-adjusted event rate per 100 PYE; EAER* = (number of events/PYE)*100; GEE = generalized estimating equations; NEst = not estimable; PYE = patient-years of exposure; TE = treatment-emergent; TEAE = treatment-emergent adverse event

Adverse events were coded according to the Medical Dictionary for Regulatory Activities, Version 22.1.

Severity grades were defined by the Common Terminology Criteria for Adverse Events, Version 4.03.

Death includes any death that occurred during the study.

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

Common adverse events

Summaries of EAIRs for common AEs by preferred term (PT) reported in Cohort 1 (Cohort A Induction Study and Cohort B Induction Study Combined) and Cohort 2 (Maintenance Study) are provided in the tables below along with a summary of EAERs for common AEs by PT in Cohort 3.

Table 52. Exposure-Adjusted Incidence Rates of Adverse Events by Preferred Term (≥ 10/100 PYE in Any Treatment Group) Among Subjects in Cohort 1 (Cohort A Induction Study and Cohort B Induction Study Combined; Safety Analysis Set, treatment duration 11 weeks)

Preferred Term	Filgotinib 200 mg (N=507)	Filgotinib 100 mg (N=562)	Placebo (N=279)	EAIR Difference (95% CI)		
	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	Filgotinib 200 mg vs. Placebo	Filgotinib 100 mg vs. Placebo	Filgotinib 200 mg vs. 100 mg
Subjects with TEAE	271/69.3	282/80.0	156/37.0			

Preferred Term	Filgotinib 200 mg (N=507)	Filgotinib 100 mg (N=562)	Placebo (N=279)	EAIR Difference (95% CI)		
	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	Filgotinib 200 mg vs. Placebo	Filgotinib 100 mg vs. Placebo	Filgotinib 200 mg vs. 100 mg
	391.0 (345.8,440.4)	352.4 (312.5,396.0)	422.1 (358.5,493.8)	-31.1 (-115.8,49.5)	-69.7 (-151.8,7.4)	38.6 (-24.2,102.1)
Nasopharyngitis	27/105.6	29/116.8	13/57.6			
	25.6 (16.9,37.2)	24.8 (16.6,35.7)	22.6 (12.0,38.6)	3.0 (-15.2,18.7)	2.3 (-15.7,17.4)	0.7 (-13.2,15.0)
Headache	30/104.4	23/116.9	15/57.4			
	28.7 (19.4,41.0)	19.7 (12.5,29.5)	26.1 (14.6,43.1)	2.6 (-16.8,19.4)	-6.4 (-24.9,8.7)	9.1 (-4.5,23.3)
Colitis ulcerative	26/106.8	21/117.8	18/57.4			
	24.3 (15.9,35.7)	17.8 (11.0,27.2)	31.3 (18.6,49.5)	-7.0 (-27.1,10.1)	-13.5 (-32.9,2.3)	6.5 (-6.1,19.7)
Anaemia	19/106.2	22/116.9	15/57.9			
	17.9 (10.8,27.9)	18.8 (11.8,28.5)	25.9 (14.5,42.7)	-8.0 (-26.3,7.2)	-7.1 (-25.3,7.9)	-0.9 (-12.9,11.3)
Nausea	15/106.5	19/117.2	7/58.1			
	14.1 (7.9,23.2)	16.2 (9.8,25.3)	12.0 (4.8,24.8)	2.0 (-12.2,13.7)	4.2 (-10.2,15.8)	-2.1 (-13.1,9.1)
Abdominal pain	12/107.6	10/118.8	11/57.4			
	11.2 (5.8,19.5)	8.4 (4.0,15.5)	19.2 (9.6,34.3)	-8.0 (-24.1,4.7)	-10.8 (-26.5,1.2)	2.7 (-6.1,12.1)
Arthralgia	8/108.1	14/118.1	9/58.2			
	7.4 (3.2,14.6)	11.9 (6.5,19.9)	15.5 (7.1,29.4)	-8.1 (-22.6,3.0)	-3.6 (-18.5,8.0)	-4.5 (-13.5,4.5)
Upper respiratory tract infection	15/106.7	6/119.6	5/58.7			
	14.1 (7.9,23.2)	5.0 (1.8,10.9)	8.5 (2.8,19.9)	5.5 (-7.4,16.3)	-3.5 (-15.3,4.7)	9.0 (0.5,18.7)
Pyrexia	11/107.6	4/119.8	9/58.3			
	10.2 (5.1,18.3)	3.3 (0.9,8.6)	15.4 (7.1,29.3)	-5.2 (-20.0,6.4)	-12.1 (-26.2,-2.2)	6.9 (-0.4,15.3)
Vomiting	8/108.0	7/119.5	8/58.3			

Preferred Term	Filgotinib 200 mg (N=507)	Filgotinib 100 mg (N=562)	Placebo (N=279)	EAIR Difference (95% CI)		
	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	n/PYE EAIR (95% CI)	Filgotinib 200 mg vs. Placebo	Filgotinib 100 mg vs. Placebo	Filgotinib 200 mg vs. 100 mg
	7.4 (3.2,14.6)	5.9 (2.4,12.1)	13.7 (5.9,27.1)	-6.3 (-20.3,4.3)	-7.9 (-21.7,2.1)	1.6 (-6.0,9.6)
Asthenia	5/108.1	5/119.6	9/58.3			
	4.6 (1.5,10.8)	4.2 (1.4,9.8)	15.4 (7.1,29.3)	-10.8 (-25.0,-0.4)	-11.2 (-25.4,-1.2)	0.4 (-5.9,7.2)

Table 53. Exposure-Adjusted Incidence Rates of Adverse Events by Preferred Term (≥ 10/100 PYE in Any Treatment Group) Among Subjects in Cohort 2 (Maintenance Study; Safety Analysis Set, treatment duration 47 weeks)

Preferred Term	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg				Induction Placebo
	Maintenance Filgotinib 200 mg (N=202) n/PYE EAIR (95% CI)	Maintenance Placebo (N=99) n/PYE EAIR (95% CI)	Maintenance Filgotinib 200 mg vs. Placebo EAIR Diff (95% CI)	Maintenance Filgotinib 100 mg (N=179) n/PYE EAIR (95% CI)	Maintenance Placebo (N=91) n/PYE EAIR (95% CI)	Maintenance Filgotinib 100 mg vs. Placebo EAIR Diff (95% CI)	Maintenance Filgotinib 200 mg vs. 100 mg EAIR Diff (95% CI)	Maintenance Placebo (N=93) n/PYE EAIR (95% CI)
Subjects with TEAE	134/80.1	57/31.4		107/72.7	60/30.3			57/40.6
	167.4	181.4	-14.0	147.2	198.3	-51.1	20.2	140.2
	(140.2,198.2)	(137.4,235.0)	(-74.1,39.8)	(120.7,177.9)	(151.3,255.3)	(-113.9,5.0)	(-20.8,60.9)	(106.2,181.7)
Colitis ulcerative	21/150.6	18/54.1		19/118.3	16/49.8			10/67.8
	13.9	33.3	-19.3	16.1	32.1	-16.1	-2.1	14.7
	(8.6,21.3)	(19.7,52.6)	(-39.4,-3.9)	(9.7,25.1)	(18.4,52.2)	(-37.1,0.4)	(-12.6,7.6)	(7.1,27.1)
Nasopharyngitis	22/142.7	6/52.2		12/115.0	6/50.9			5/66.6
	15.4	11.5	3.9	10.4	11.8	-1.4	5.0	7.5
	(9.7,23.3)	(4.2,25.0)	(-10.8,14.7)	(5.4,18.2)	(4.3,25.7)	(-16.1,9.4)	(-4.7,14.4)	(2.4,17.5)
Arthralgia	8/149.8	7/52.2		6/117.7	3/51.1			4/67.3

Preferred Term	Induction Filgotinib 200 mg			Induction Filgotinib 100 mg				Induction Placebo
	Maintenance Filgotinib 200 mg (N=202) n/PYE EAIR (95% CI)	Maintenance Placebo (N=99) n/PYE EAIR (95% CI)	Maintenance Filgotinib 200 mg vs. Placebo EAIR Diff (95% CI)	Maintenance Filgotinib 100 mg (N=179) n/PYE EAIR (95% CI)	Maintenance Placebo (N=91) n/PYE EAIR (95% CI)	Maintenance Filgotinib 100 mg vs. Placebo EAIR Diff (95% CI)	Maintenance Filgotinib 200 mg vs. 100 mg EAIR Diff (95% CI)	Maintenance Placebo (N=93) n/PYE EAIR (95% CI)
	5.3	13.4	-8.1	5.1	5.9	-0.8	0.2	5.9
	(2.3,10.5)	(5.4,27.6)	(-22.6,1.5)	(1.9,11.1)	(1.2,17.1)	(-12.5,6.8)	(-6.5,6.4)	(1.6,15.2)
Abdominal pain	8/150.9	6/53.2		6/117.1	2/50.9			4/67.6
	5.3	11.3	-6.0	5.1	3.9	1.2	0.2	5.9
	(2.3,10.4)	(4.1,24.6)	(-19.6,2.8)	(1.9,11.1)	(0.5,14.2)	(-9.6,8.1)	(-6.6,6.3)	(1.6,15.2)

Table 54. Exposure-Adjusted Event Rates of Adverse Events by Preferred Term (≥ 4/100 PYE in Any Treatment Group) Among Subjects in Cohort 3 (GS-US-418-3898 and GS-US-418-3899 Combined; Safety Analysis Set)

Preferred Term	Non-Model-based descriptive statistics			Model-based EAER Ratio (95% CI)		
	Filgotinib 200 mg (N=971) (PYE=1233.9) n(EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n(EAER*)	Placebo (N=469) (PYE=324.7) n(EAER*)	Filgotinib 200 mg vs. Placebo	Filgotinib 100 mg vs. Placebo	Filgotinib 200 mg vs. 100 mg
Number of TEAEs	3280 (265.8)	1182 (318.9)	1004 (309.2)	0.8 (0.7,0.9)	0.9 (0.7,1.0)	0.9 (0.8,1.0)
Colitis ulcerative	213 (17.3)	82 (22.1)	86 (26.5)	0.6 (0.4,0.7)	0.8 (0.6,1.1)	0.7 (0.5,0.9)
Nasopharyngitis	186 (15.1)	56 (15.1)	37 (11.4)	1.1 (0.7,1.6)	1.0 (0.6,1.6)	1.0 (0.7,1.5)
Headache	93 (7.5)	50 (13.5)	39 (12.0)	0.6 (0.3,1.1)	0.8 (0.4,1.6)	0.8 (0.5,1.2)
Upper respiratory tract infection	84 (6.8)	23 (6.2)	19 (5.9)	1.0 (0.5,1.9)	0.9 (0.4,2.0)	1.1 (0.6,2.1)
Anaemia	70 (5.7)	30 (8.1)	19 (5.9)	1.0 (0.5,1.7)	1.2 (0.6,2.3)	0.8 (0.5,1.3)

Preferred Term	Non-Model-based descriptive statistics			Model-based EAER Ratio (95% CI)		
	Filgotinib 200 mg (N=971) (PYE=1233.9) n(EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n(EAER*)	Placebo (N=469) (PYE=324.7) n(EAER*)	Filgotinib 200 mg vs. Placebo	Filgotinib 100 mg vs. Placebo	Filgotinib 200 mg vs. 100 mg
Arthralgia	69 (5.6)	25 (6.7)	25 (7.7)	0.6 (0.4,0.9)	0.7 (0.4,1.3)	0.8 (0.5,1.3)
Abdominal pain	46 (3.7)	25 (6.7)	33 (10.2)	0.3 (0.2,0.6)	0.5 (0.3,1.0)	0.6 (0.3,1.1)
Nausea	52 (4.2)	30 (8.1)	13 (4.0)	0.9 (0.5,1.8)	1.5 (0.7,3.0)	0.6 (0.4,1.1)
Pyrexia	49 (4.0)	12 (3.2)	18 (5.5)	0.6 (0.3,1.2)	0.5 (0.2,1.1)	1.3 (0.6,2.7)
Back pain	47 (3.8)	13 (3.5)	13 (4.0)	1.0 (0.5,2.0)	0.8 (0.4,2.0)	1.2 (0.6,2.3)
Hypertension	36 (2.9)	12 (3.2)	13 (4.0)	0.7 (0.3,1.4)	0.7 (0.3,1.7)	1.0 (0.5,2.2)
Urinary tract infection	49 (4.0)	6 (1.6)	5 (1.5)	2.4 (0.9,6.3)	0.8 (0.2,2.8)	3.1 (1.1,8.5)
Hypophosphataemia	39 (3.2)	15 (4.0)	5 (1.5)	1.5 (0.5,4.5)	2.1 (0.6,7.5)	0.7 (0.3,1.7)
Lymphopenia[a]	23 (1.9)	15 (4.0)	16 (4.9)	0.4 (0.1,1.5)	0.8 (0.2,3.3)	0.5 (0.2,1.3)
Vomiting	27 (2.2)	11 (3.0)	15 (4.6)	0.5 (0.2,1.2)	0.5 (0.2,1.4)	1.0 (0.4,2.2)
Diarrhoea[a]	24 (1.9)	12 (3.2)	13 (4.0)	0.4 (0.2,0.8)	0.7 (0.2,1.7)	0.6 (0.2,1.5)

Serious adverse event/deaths/other significant events

A total of 3 deaths occurred: 2 deaths were reported in Cohort 2 (maintenance phase), both for subjects in the filgotinib 200 mg group (left ventricular failure in 1 subject and asthma in 1 subject), and 1 additional death was reported in Cohort 3 (overall safety data) for a subject who received filgotinib 100 mg in Study GS-US-418-3898 and filgotinib 200 mg in Study GS-US-418-3899 (myocardial infarction and ischemic stroke). The details of the deaths are as follows:

- Subject A: A medical history of chronic bronchitis, nonalcoholic fatty liver disease, cystic lung disease, and deep vein thrombosis died from left ventricular failure on Day 81 of the Maintenance Study in Study GS-US-418-3898. The cause of death was determined based upon the autopsy findings, which revealed coronary artery arteriosclerosis and left ventricular failure.

- Subject B: A medical history of asthma, ankylosing spondylitis, hypertension, and nasal polypectomy died from asthma on Day 302 of the Maintenance Study in Study GS-US-418-3898. According to the investigator, the patient saw his primary care provider for asthma which was assessed to be flaring due to allergy. Death certificate showed asthma as cause of death. No autopsy was performed.
- Subject C: An history of chronic cholecystitis, chronic pancreatitis, chronic gastritis, duodenitis, and hepatic steatosis died due to myocardial infarction and ischemic stroke on Day 343 in GS-US-418-3899. The subject was hospitalized for non-Q wave myocardial infarction on Study Day 337. During the course of hospitalization, he experienced an ischemic stroke and died on Study Day 343. Autopsy was performed which identified acute myocardial infarction as the primary cause of death. Additional post-mortem findings included aortic atherosclerosis, parietal thrombi in the apical area of the heart, and thromboembolism of the medial branch of cerebral artery, cerebral infarction, and cerebral oedema. The primary causes of death were determined to be myocardial infarction and ischemic stroke.

The MAH presented in the responses to the RSI two additional deaths:

- Subject D died from COVID-19 infection, two years after starting treatment with filgotinib 200 mg. Although filgotinib does increase the risk for infections, firm conclusions on potential causality in this case with an ongoing pandemic cannot be determined.
- Subject E treated with open-label filgotinib 200 mg for approximately 1,5 years, who died from COVID-19 infection. Filgotinib had been discontinued around 1 month earlier due to endometrial cancer. Causality with filgotinib is less likely because treatment had been discontinued, although the exact timeframe is not clear.

Adverse events of special interest

Adverse events of interest included all infections; serious infections; herpes zoster infections; opportunistic infections; malignancy (excluding nonmelanoma skin cancer [NMSC]); NMSC; gastrointestinal (GI) perforations; and thromboembolic events (including venous thrombosis, pulmonary embolism (PE), arterial thrombosis, and cerebrovascular events).

A summary of EAERs for AEIs in Cohort 3 is provided in the table below.

Table 55. Summary of Exposure-Adjusted Event Rates of Adverse Events of Interest Among Subjects in Cohort 3 (GS-US-418-3898 and GS-US-418-3899 Combined; Safety Analysis Set)

	Non-model-based Descriptive Statistics			**Model-based EAER Ratio (95% CI)**		
Adverse Events of Interest	**Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)**	**Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)**	**Placebo (N=469) (PYE=324.7) n (EAER*)**	**Filgotinib 200 mg vs Placebo**	**Filgotinib 100 mg vs Placebo**	**Filgotinib 200 mg vs 100 mg**
Infections						

Adverse Events of Interest	Non-model-based Descriptive Statistics			Model-based EAER Ratio (95% CI)		
	Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)	Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)	Placebo (N=469) (PYE=324.7) n (EAER*)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs 100 mg
All Infections	857 (69.5)	217 (58.5)	198 (61.0)	1.0 (0.8,1.2)	0.8 (0.7,1.1)	1.2 (0.9, 1.4)
Serious Infections	27 (2.2)	13 (3.5)	7 (2.2)	1.0 (0.3,2.8)	2.0 (0.6,6.9)	0.5 (0.2,1.2)
Herpes Zoster	22 (1.8)	1 (0.3)	1 (0.3)	5.3 (0.7,37.7)	0.8 (0.1,12.5)	6.2 (0.8,47.4)
Opportunistic Infections	3 (0.2)	1 (0.3)	0	NEst	NEst	0.7 (0.1,7.3)
Malignancies Excluding NMSC	10 (0.8)	5 (1.3)	0	NEst	NEst	0.7 (0.2,3.0)
NMSC	8 (0.6)	3 (0.8)	1 (0.3)	1.6 (0.2,10.8)	3.6 (0.2,79.2)	0.4 (0.0,4.8)
Gastrointestinal Perforations	0	0	1 (0.3)	NEst	NEst	NEst
Thromboembolic Events						
Venous Thrombosis	0	0	3 (0.9)	NEst	NEst	NEst
Pulmonary Embolism	1 (0.1)	0	0	NEst	NEst	NEst
Arterial Thrombosis	3 (0.2)	1 (0.3)	0	NEst	NEst	NEst
Cerebrovascular Events	3 (0.2)	2 (0.5)	1 (0.3)	1.0 (0.1,12.8)	1.9 (0.1,35.2)	0.5 (0.1,2.8)

Infections

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

The most common infections were nasopharyngitis, upper respiratory tract infection, and urinary tract infection. The most common serious infections were appendicitis, cellulitis and pneumonia (Table 56).

Table 56. Summary of Exposure-Adjusted Event Rates of Serious Infection Among Subjects in Cohort 3 (GS-US-418-3898 and GS-US-418-3899 Combined; Safety Analysis Set)

	Non-model-based Descriptive Statistics			**Model-based EAER Ratio (95% CI)**		
Preferred Term	**Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)**	**Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)**	**Placebo (N=469) (PYE=324.7) n (EAER*)**	**Filgotinib 200 mg vs Placebo**	**Filgotinib 100 mg vs Placebo**	**Filgotinib 200 mg vs 100 mg**
Number of Treatment-Emergent Adverse Events of Serious Infections	27 (2.2)	13 (3.5)	7 (2.2)	1.0 (0.3,2.8)	2.0 (0.6,6.9)	0.5 (0.2,1.2)
Appendicitis [#,$]	1 (0.1)	4 (1.1)	0	NEst	NEst	0.1 (0.0,1.2)
Cellulitis [#]	2 (0.2)	2 (0.5)	1 (0.3)	0.6 (0.1,7.1)	4.4 (0.1,168.1)	0.1 (0.0,2.0)
Pneumonia [#,$]	4 (0.3)	0	1 (0.3)	1.4 (0.1,12.6)	NEst	NEst
Gastroenteritis viral	1 (0.1)	0	2 (0.6)	NEst	NEst	NEst
Anal abscess	1 (0.1)	1 (0.3)	0	NEst	NEst	NEst
Clostridium difficile infection	2 (0.2)	0	0	NEst	NEst	NEst
Diverticulitis	2 (0.2)	0	0	NEst	NEst	NEst
Infectious pleural effusion	2 (0.2)	0	0	NEst	NEst	NEst

	Non-model-based Descriptive Statistics			Model-based EAER Ratio (95% CI)		
Preferred Term	**Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)**	**Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)**	**Placebo (N=469) (PYE=324.7) n (EAER*)**	**Filgotinib 200 mg vs Placebo**	**Filgotinib 100 mg vs Placebo**	**Filgotinib 200 mg vs 100 mg**
Paronychia	0	2 (0.5)	0	NEst	NEst	NEst
Sepsis	0	2 (0.5)	0	NEst	NEst	NEst
Acute hepatitis B	0	0	1 (0.3)	NEst	NEst	NEst
Bursitis infective	1 (0.1)	0	0	NEst	NEst	NEst
Campylobacter gastroenteritis	0	0	1 (0.3)	NEst	NEst	NEst
Dengue fever	1 (0.1)	0	0	NEst	NEst	NEst
Gastroenteritis	0	1 (0.3)	0	NEst	NEst	NEst
Gastroenteritis clostridial	1 (0.1)	0	0	NEst	NEst	NEst
Herpes zoster	1 (0.1)	0	0	NEst	NEst	NEst
Lung abscess	1 (0.1)	0	0	NEst	NEst	NEst
Osteomyelitis	0	0	1 (0.3)	NEst	NEst	NEst
Peritonitis	1 (0.1)	0	0	NEst	NEst	NEst
Peritonsillar abscess	1 (0.1)	0	0	NEst	NEst	NEst
Pyelonephritis acute	1 (0.1)	0	0	NEst	NEst	NEst
Renal abscess	1 (0.1)	0	0	NEst	NEst	NEst
Septic pulmonary embolism	1 (0.1)	0	0	NEst	NEst	NEst

	Non-model-based Descriptive Statistics			Model-based EAER Ratio (95% CI)		
Preferred Term	**Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)**	**Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)**	**Placebo (N=469) (PYE=324.7) n (EAER*)**	**Filgotinib 200 mg vs Placebo**	**Filgotinib 100 mg vs Placebo**	**Filgotinib 200 mg vs 100 mg**
Staphylococcal infection	0	1 (0.3)	0	NEst	NEst	NEst
Subcutaneous abscess	1 (0.1)	0	0	NEst	NEst	NEst
Urinary tract infection	1 (0.1)	0	0	NEst	NEst	NEst

Malignancies excluding nonmelanoma skin cancers

A summary of EAERs for malignancies excluding NMSC in Cohort 3 is provided in Table 57.

Table 57. Summary of Exposure-Adjusted Event Rates of Malignancies Excluding Nonmelanoma Skin Cancers Among Subjects in Cohort 3 (GS-US-418-3898 and GS-US-418-3899 Combined; Safety Analysis Set)

	Non-model-based Descriptive Statistics			Model- based EAER Ratio (95% CI)		
Preferred Term	**Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)**	**Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)**	**Placebo (N=469) (PYE=324.7) n (EAER*)**	**Filgotinib 200 mg vs Placebo**	**Filgotinib 100 mg vs Placebo**	**Filgotinib 200 mg vs 100 mg**
Number of Treatment-Emergent Adverse Events of Malignancies Excluding Nonmelanoma Skin Cancers [$]	10 (0.8)	5 (1.3)	0	NEst	NEst	0.7 (0.2,3.0)
Colon cancer [#,$]	1 (0.1)	2 (0.5)	0	NEst	NEst	0.1 (0.0,0.5)
Adenocarcinoma of colon	2 (0.2)	0	0	NEst	NEst	NEst

	Non-model-based Descriptive Statistics			Model- based EAER Ratio (95% CI)		
Preferred Term	**Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)**	**Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)**	**Placebo (N=469) (PYE=324.7) n (EAER*)**	**Filgotinib 200 mg vs Placebo**	**Filgotinib 100 mg vs Placebo**	**Filgotinib 200 mg vs 100 mg**
Breast cancer	1 (0.1)	0	0	NEst	NEst	NEst
Clear cell renal cell carcinoma	1 (0.1)	0	0	NEst	NEst	NEst
Malignant melanoma	1 (0.1)	0	0	NEst	NEst	NEst
Metastatic carcinoid tumour	1 (0.1)	0	0	NEst	NEst	NEst
Oesophageal adenocarcinoma	1 (0.1)	0	0	NEst	NEst	NEst
Papillary renal cell carcinoma	0	1 (0.3)	0	NEst	NEst	NEst
Plasma cell myeloma	0	1 (0.3)	0	NEst	NEst	NEst
Prostate cancer	1 (0.1)	0	0	NEst	NEst	NEst
Renal cell carcinoma	0	1 (0.3)	0	NEst	NEst	NEst
Uterine leiomyosarcoma	1 (0.1)	0	0	NEst	NEst	NEst

EAER = exposure-adjusted event rate per 100 PYE; EAER* = (number of events/PYE)*100; GEE = generalized estimating equations; NEst = not estimable; PYE = patient-years of exposure

Adverse events were coded according to Medical Dictionary for Regulatory Activities (MedDRA), Version 22.1.

Adverse events of malignancy excluding nonmelanoma skin cancer were defined by the MedDRA Search Term List developed by Gilead.

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

$ Data contributing to the zero-event count for only 1 treatment group were removed from the model-based analysis.

Data contributing to the zero-event count for a period across all treatment groups were removed from the model-based analysis.

Venous and arterial thromboembolism

No venous thrombosis was reported in subjects in the filgotinib 200 mg or filgotinib 100 mg treatment groups and 3 events of venous thrombosis were reported in the placebo group. There was 1 event of pulmonary embolism reported for a subject in the filgotinib 200 mg group, and no cases in the other treatment groups.

A summary of EAERs for arterial thrombosis in Cohort 3 is provided in Table 58.

Table 58. Summary of Exposure-Adjusted Event Rates of Arterial Thrombosis Among Subjects in Cohort 3 (GS-US-418-3898 and GS-US-418-3899 Combined; Safety Analysis Set)

	Non-model-based Descriptive Statistics			**Model-based EAER Ratio (95% CI)**		
Preferred Term	**Filgotinib 200 mg (N=971) (PYE=1233.9) n (EAER*)**	**Filgotinib 100 mg (N=583) (PYE=370.7) n (EAER*)**	**Placebo (N=469) (PYE=324.7) n (EAER*)**	**Filgotinib 200 mg vs Placebo**	**Filgotinib 100 mg vs Placebo**	**Filgotinib 200 mg vs 100 mg**
Number of Treatment-Emergent Adverse Events of Arterial Thrombosis	3 (0.2)	1 (0.3)	0	NEst	NEst	NEst
Myocardial infarction	2 (0.2)	0	0	NEst	NEst	NEst
Ischaemic stroke	1 (0.1)	0	0	NEst	NEst	NEst
Transient ischaemic attack	0	1 (0.3)	0	NEst	NEst	NEst

EAER = exposure-adjusted event rate per 100 PYE; EAER* = (number of events/PYE)*100; GEE = generalized estimating equations; NEst = not estimable; PYE = patient-years of exposure

Adverse events were coded according to Medical Dictionary for Regulatory Activities (MedDRA), Version 22.1.

Adverse events of arterial thrombosis were defined by the embolic and thrombotic events, arterial Standardized MedDRA Queries. Model-based EAER ratio and corresponding 95% CI were estimated using a GEE model for longitudinal count data including treatment group adjusted for treatment period and patient population (biologic naive or biologic experienced) with an offset of natural log of exposure time.

Cerebrovascular events

Three events were reported in subjects in the filgotinib 200 mg group (EAER = 0.2/100 PYE), a Grade 2 brachiocephalic arteriosclerosis, a Grade 3 carotid artery stenosis, and a Grade 5 ischemic stroke; 2 events were reported in subjects in the filgotinib 100 mg group (EAER = 0.5/100 PYE), a Grade 4 spinal cord infarction and a Grade 2 transient ischemic attack; and 1 event was reported in subjects in the placebo group (EAER = 0.3/100 PYE), a Grade 4 cerebrovascular accident. The events

of transient ischemic attack and ischemic stroke were also reported under the arterial thrombosis category.

Laboratory findings

Haematological parameters

Haemoglobin and platelets

Change from baseline in haemoglobin values during induction and maintenance is showed below.

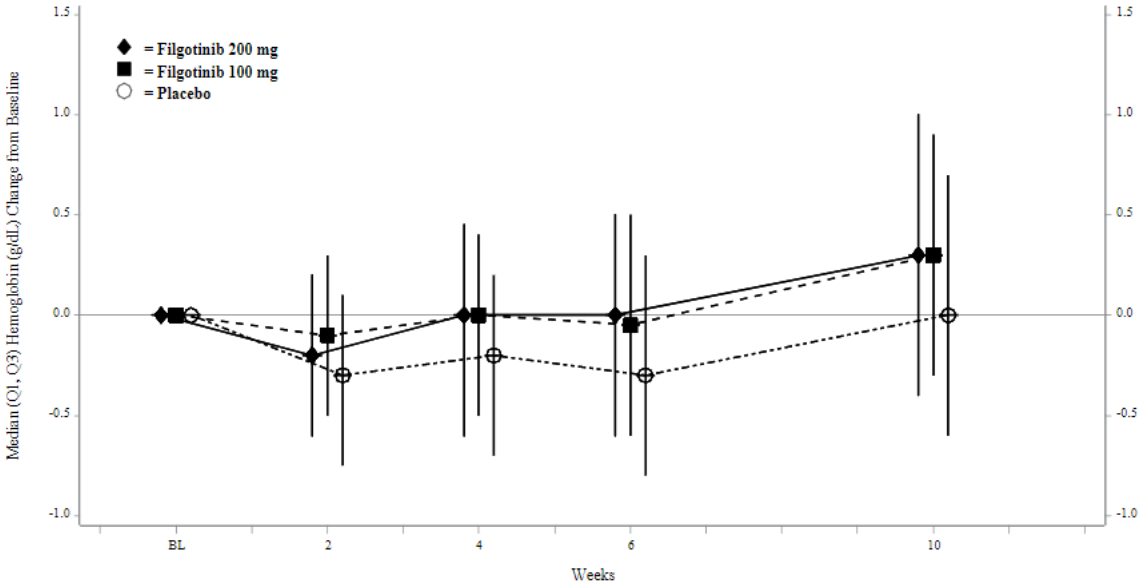


Figure 43. Median (Q1, Q3) Hemoglobin (g/dL) Change from Baseline by Visit Induction Studies: Cohorts A and B Safety Analysis Set

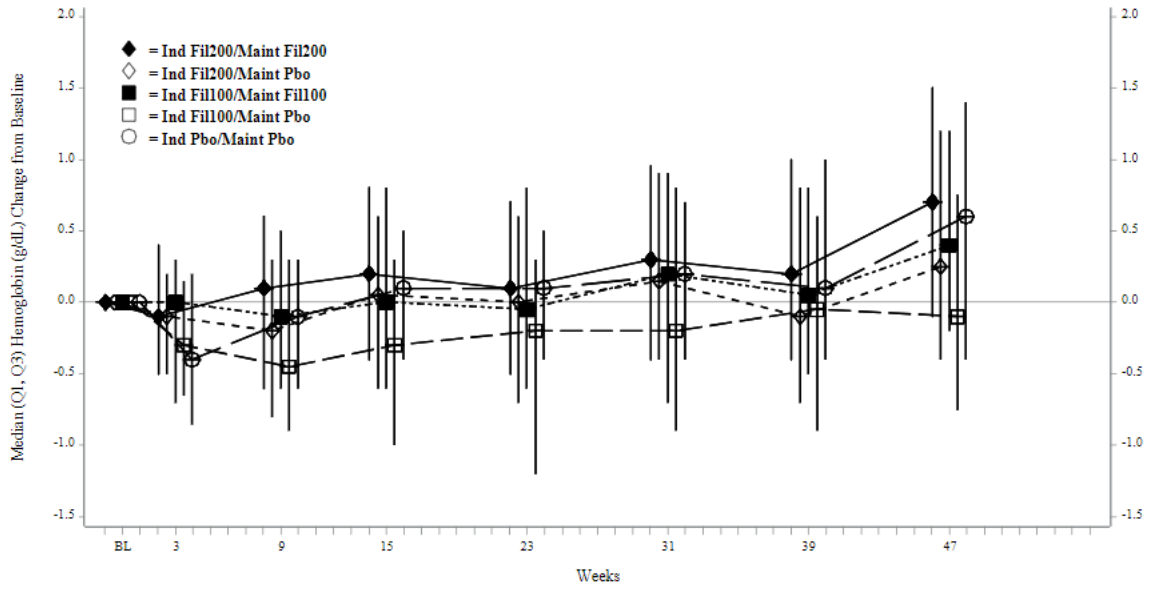


Figure 44. Median (Q1, Q3) Hemoglobin (g/dL) Change from Maintenance Baseline by Visit Maintenance Study Safety Analysis Set

Neutrophils

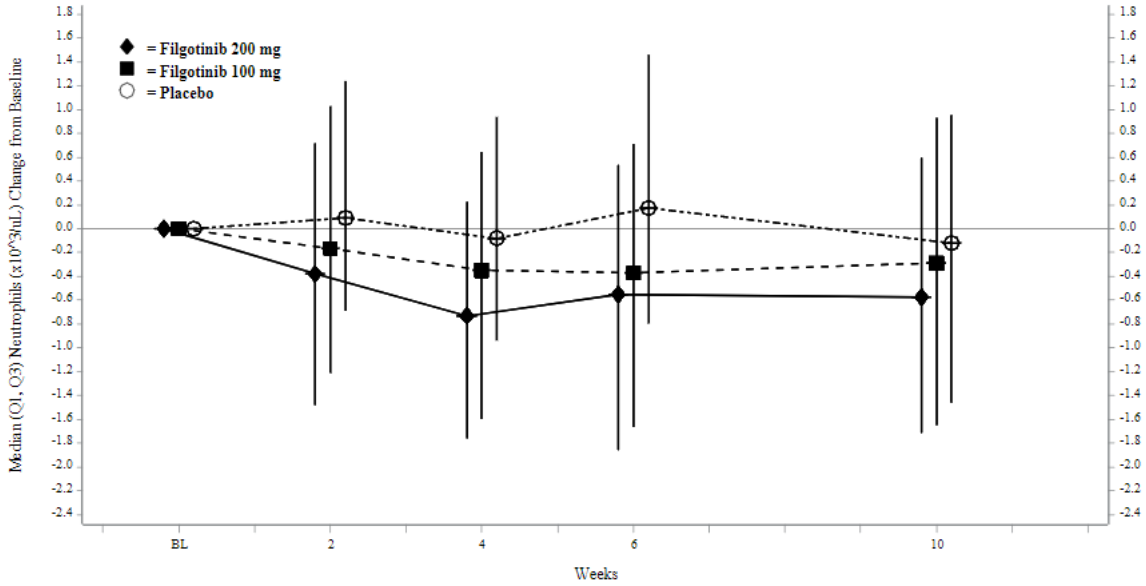


Figure 45. Median (Q1, Q3) Neutrophils (x10^3 /uL) Change from Baseline by Visit Induction Studies: Cohorts A and B Safety Analysis Set

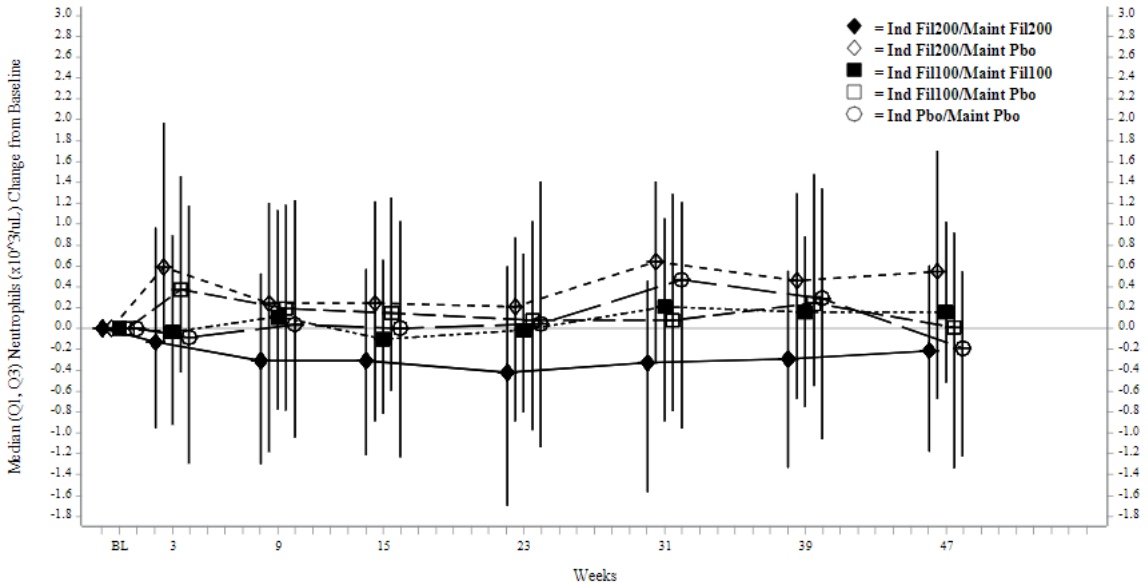


Figure 46. Median (Q1, Q3) Neutrophils (x10^3 /uL) Change from Maintenance Baseline by Visit Maintenance Study Safety Analysis Set

Chemistry

Immunoglobulins

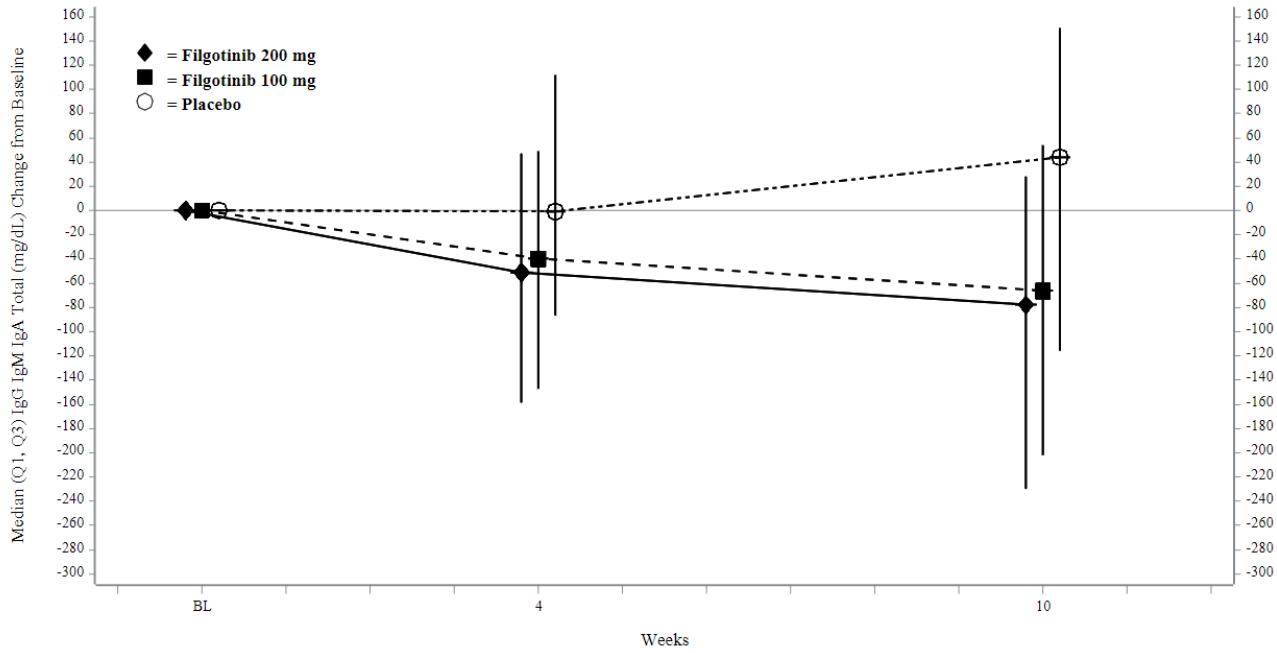


Figure 47. Median (Q1, Q3) Total Immunoglobulin (mg/dL) Change from Baseline by Visit Induction Studies: Cohorts A and B Safety Analysis Set

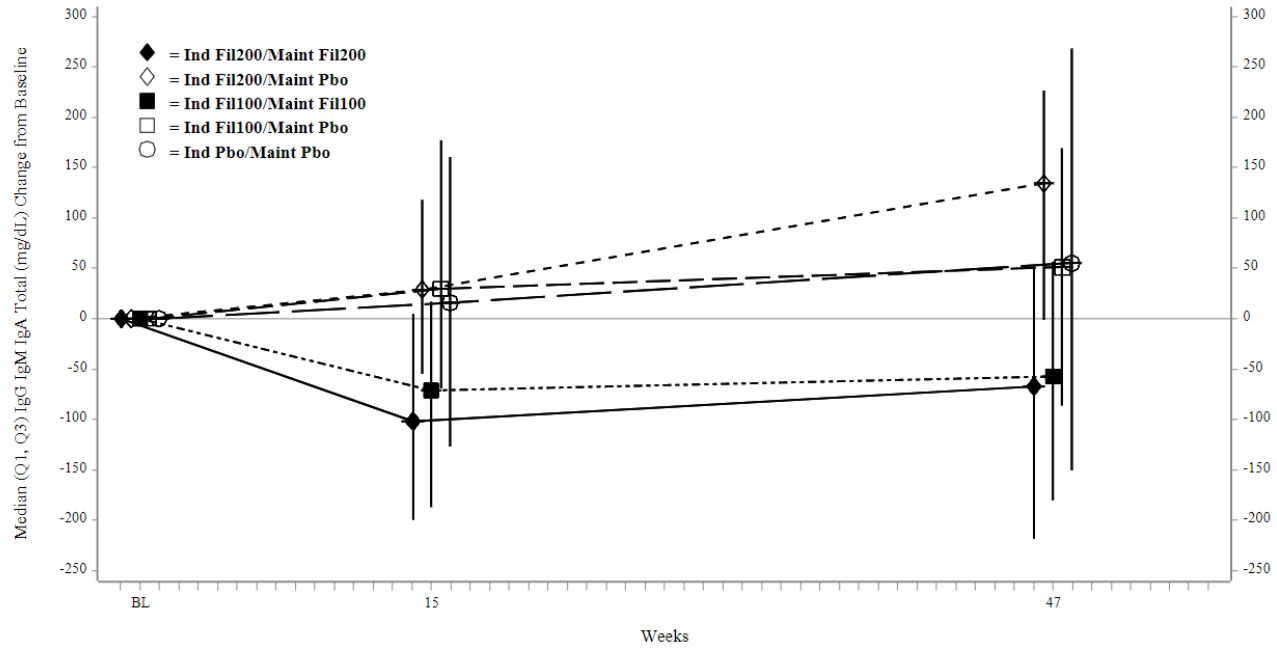


Figure 48. Median (Q1, Q3) Total Immunoglobulin (mg/dL) Change from Maintenance Baseline by Visit Maintenance Study Safety Analysis Set

Liver transaminases

Change in ALT and AST levels are shown below.

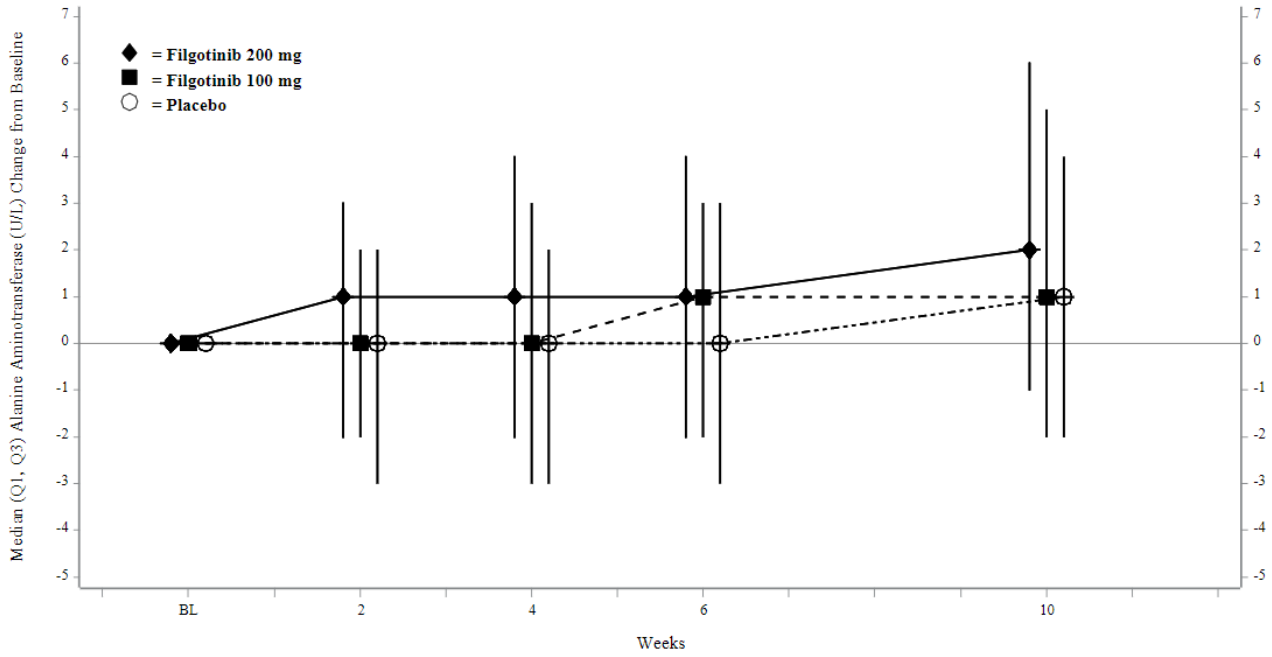


Figure 49. Median (Q1, Q3) Alanine Aminotransferase (ALT, U/L) Change from Baseline by Visit Induction Studies: Cohorts A and B Safety Analysis Set

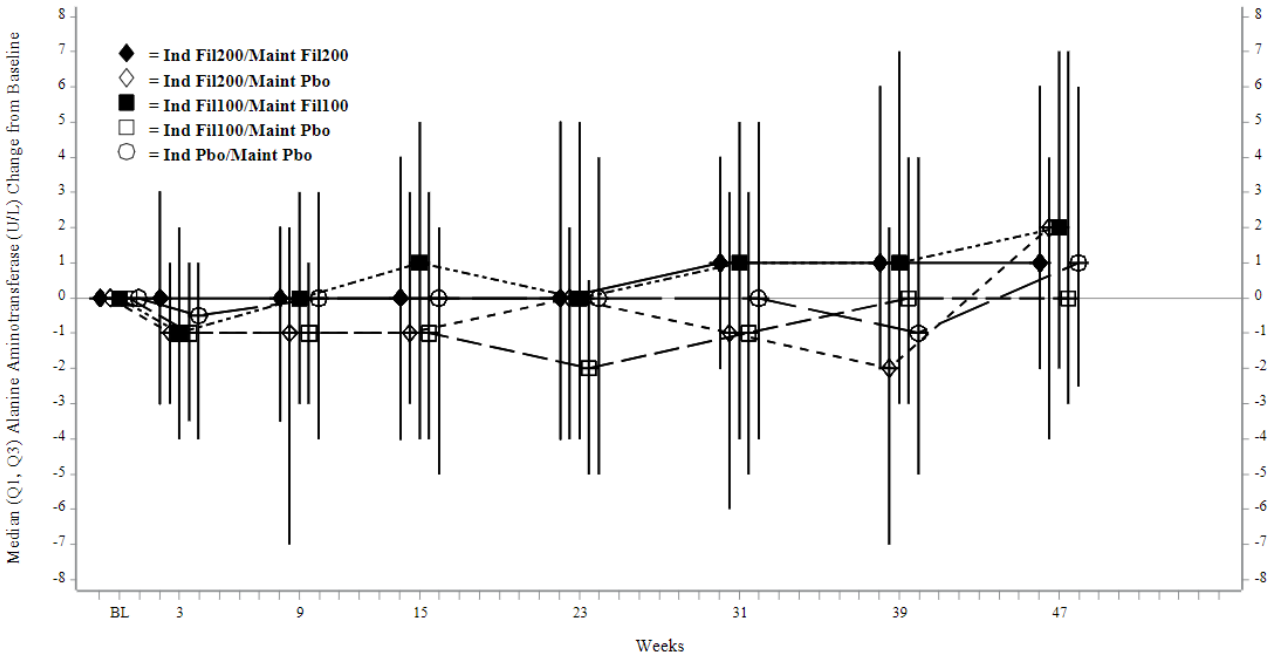


Figure 50. Median (Q1, Q3) Alanine Aminotransferase (ALT, U/L) Change from Maintenance Baseline by Visit Maintenance Study Safety Analysis Set

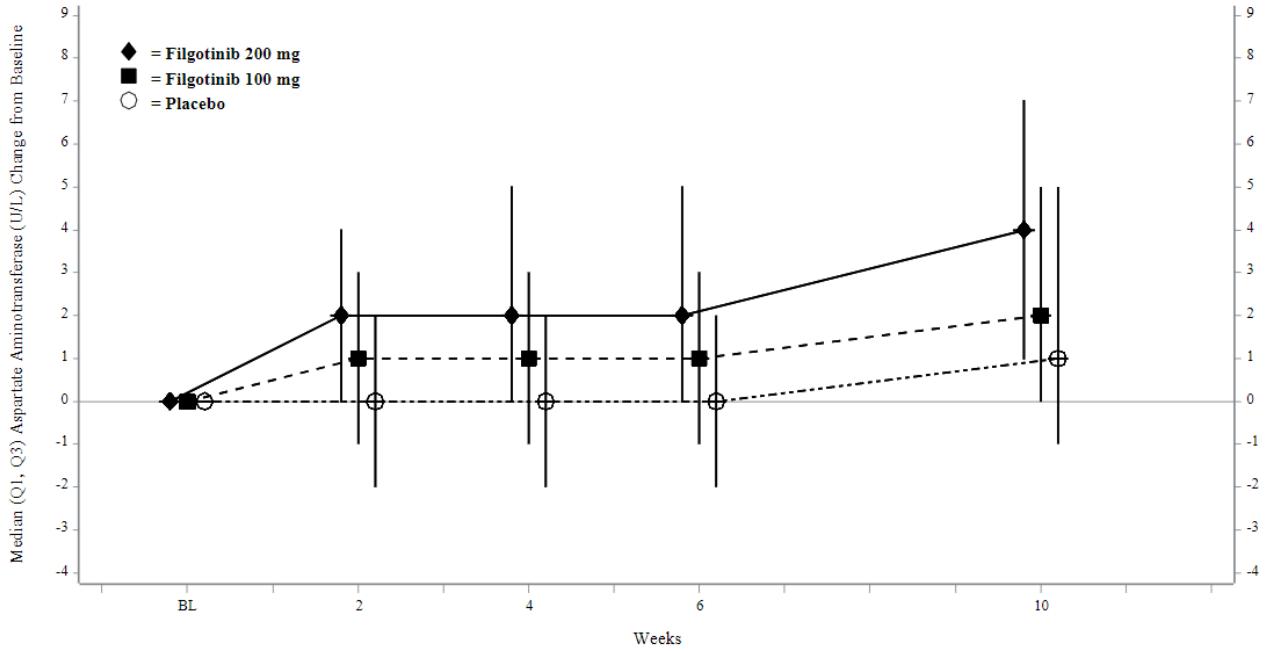


Figure 51. Median (Q1, Q3) Aspartate Aminotransferase (AST, U/L) Change from Baseline by Visit Induction Studies: Cohorts A and B Safety Analysis Set

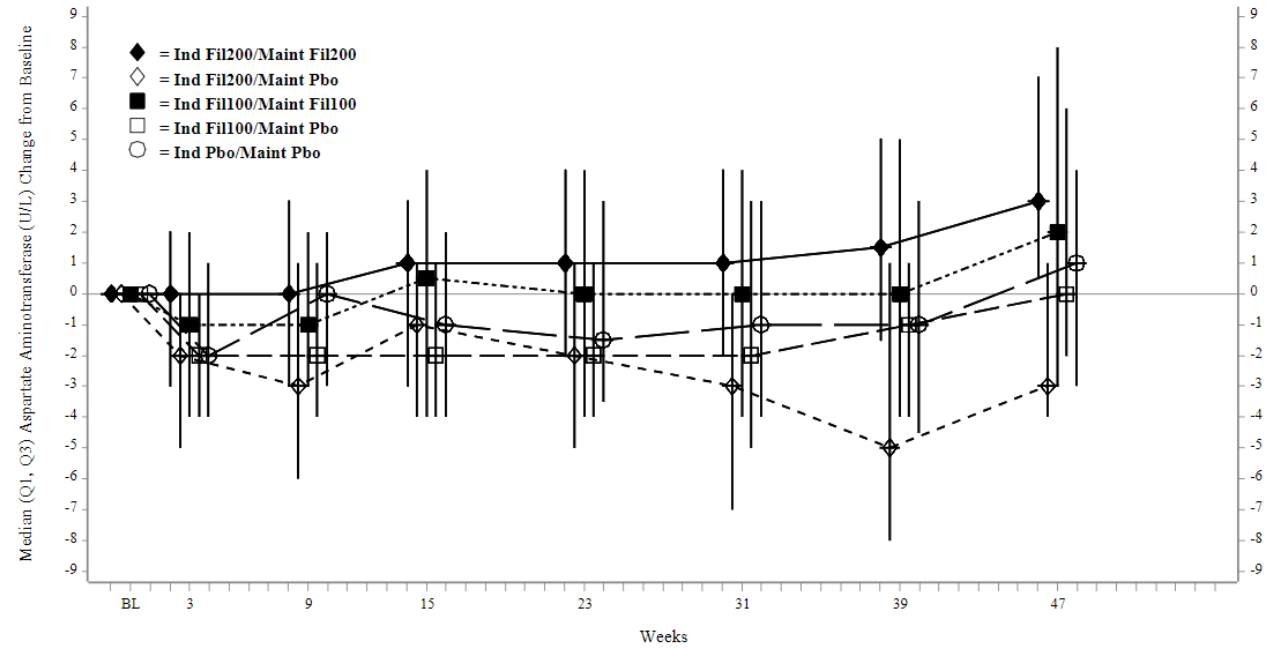


Figure 52. Median (Q1, Q3) Aspartate Aminotransferase (AST, U/L) Change from Maintenance Baseline by Visit Maintenance Study Safety Analysis Set

Vital signs, physical findings and other observations related to safety

According to the MAH, there were no clinically relevant changes from baseline in vital signs, body weight, and body mass index in Study GS-US-418-3898 and Study GS-US-418-3899.

Safety in special populations

Age

The EAIRs for the AEs, Grade 3 or higher AEs, SAEs, AEs leading to premature discontinuation of study drug, AEs leading to death, and deaths in the induction phase are summarized by age (< 65 years and ≥ 65 years).

Table 59. Subgroup Analysis: Overall Summary of Exposure Adjusted Incidence Rate of Treatment-Emergent Adverse Events, Age: < 65 Years, GS-US-418-3898 Induction Studies: Cohorts A and B - Safety Analysis Set

Subjects with any	Filgotinib 200 mg (N=477) n/PYE EAIR (95% CI)	Filgotinib 100 mg (N=525) n/PYE EAIR (95% CI)	Placebo (N=257) n/PYE EAIR (95% CI)	EAIR Difference (95% CI) Filgotinib 200 mg vs. Placebo	Filgotinib 100 mg vs. Placebo	Filgotinib 200 mg vs. 100 mg
TEAE	253/66.0 383.4 (337.6,433.7)	262/75.0 349.5 (308.5,394.5)	142/34.7 409.0 (344.5,482.0)	-25.5 (-111.8,56.2)	-59.5 (-143.3,19.2)	33.9 (-30.3,98.8)
TEAE with Grade 3 or Higher	34/98.5 34.5 (23.9,48.2)	41/108.3 37.9 (27.2,51.4)	29/51.2 56.7 (38.0,81.4)	-22.2 (-49.1,1.0)	-18.8 (-45.8,4.3)	-3.3 (-20.5,14.0)
TE Serious AE	22/100.5 21.9 (13.7,33.1)	26/109.9 23.7 (15.4,34.7)	13/53.6 24.2 (12.9,41.4)	-2.4 (-21.4,13.6)	-0.6 (-19.7,15.2)	-1.8 (-15.5,12.2)
TEAE Leading to Premature Discontinuation of Study Drug	22/100.4 21.9 (13.7,33.2)	17/110.8 15.3 (8.9,24.6)	14/53.5 26.2 (14.3,43.9)	-4.3 (-23.8,12.1)	-10.8 (-29.7,4.2)	6.6 (-5.8,19.5)
TE Serious AE Leading to Death	0	0	0			
Death	0	0	0			

Table 60. Subgroup Analysis: Overall Summary of Exposure Adjusted Incidence Rate of Treatment-Emergent Adverse Events, Age: >= 65 Years, GS-US-418-3898 Induction Studies: Cohorts A and B - Safety Analysis Set

Subjects with any	Filgotinib 200 mg (N=30) n/PYE EAIR (95% CI)	Filgotinib 100 mg (N=37) n/PYE EAIR (95% CI)	Placebo (N=22) n/PYE EAIR (95% CI)	EAIR Difference (95% CI) Filgotinib 200 mg vs. Placebo	Filgotinib 100 mg vs. Placebo	Filgotinib 200 mg vs. 100 mg
TEAE	18/3.3 541.1 (320.7,855.2)	20/5.1 395.1 (241.3,610.2)	14/2.2 625.9 (342.2,1050.1)	-84.8 (-562.9,338.5)	-230.8 (-682.1,125.2)	146.0 (-161.9,495.7)
TEAE with Grade 3 or Higher	1/6.2 16.1 (0.4,89.8)	6/7.1 84.5 (31.0,183.8)	2/4.2 47.7 (5.8,172.5)	-31.6 (-157.3,53.2)	36.7 (-99.0,144.6)	-68.3 (-168.9,22.7)
TE Serious AE	0/6.4 0.0 (0.0,57.9)	2/7.7 26.1 (3.2,94.2)	0/4.5 0.0 (0.0,82.4)	0.0 (-82.4,57.9)	26.1 (-59.4,94.2)	-26.1 (-94.2,36.2)
TEAE Leading to Premature Discontinuation of Study Drug	0/6.4 0.0 (0.0,57.9)	2/7.7 26.1 (3.2,94.2)	0/4.5 0.0 (0.0,82.4)	0.0 (-82.4,57.9)	26.1 (-59.4,94.2)	-26.1 (-94.2,36.2)
TE Serious AE Leading to Death	0	0	0			
Death	0	0	0			

Sex

The risk for AEs and SAEs was numerically slightly higher for females than for males, but the difference is not considered to be clinically meaningful and a similar pattern was observed also for placebo.

Race

As the numbers of black or African American subjects by treatment group were low (filgotinib 200 mg [N = 6]; filgotinib 100 mg [N = 9]; placebo [N = 4]) and the numbers of subjects with race other by treatment group were also low (filgotinib 200 mg [N = 19]; filgotinib 100 mg [N = 19]; placebo [N = 17]), direct comparisons of safety results among the subgroups should be interpreted with caution.

According to the MAH, during induction, the EAIRs for AEs and SAEs were generally similar between Asian and white subjects. There was no evidence to suggest an increased EAIR for AEs, Grade 3 or higher AEs, SAEs, or AEs leading to premature discontinuation of study drug for the filgotinib 200 mg and filgotinib 100 mg treatment groups compared with their respective placebo groups across the subgroups by race during maintenance.

Prior and concomitant medication

Prior TNF-α or vedolizumab failure

During induction, the EAIRs for AEs and SAEs were numerically higher for the subgroup with prior TNF-α antagonist or vedolizumab failure compared with the subgroup without prior TNF-α antagonist or vedolizumab failure. There was no evidence to suggest an increased EAIR for AEs, Grade 3 or higher AEs, SAEs, and AEs leading to premature discontinuation of study drug for the filgotinib 200 mg and filgotinib 100 mg treatment groups compared with the placebo group for both subgroups by history of prior TNF-α antagonist or vedolizumab failure.

Use of Systemic Corticosteroids or Immunomodulators at Baseline

During induction, the EAIRs for AEs and SAEs were generally similar among the subgroups by use of systemic corticosteroids or immunomodulators at induction baseline.

According to the MAH, there was no evidence to suggest an increased EAIR for AEs, Grade 3 or higher AEs, SAEs, and AEs leading to premature discontinuation of study drug for the filgotinib 200 mg and filgotinib 100 mg treatment groups compared with the placebo group across the subgroups by use of systemic corticosteroids or immunomodulators at induction baseline in Cohort 1.

During maintenance, the EAIRs for AEs and SAEs were generally similar among the subgroups by use of systemic corticosteroids or immunomodulators at maintenance baseline.

According to the MAH, there was no evidence to suggest an increased EAIR for AEs, Grade 3 or higher AEs, SAEs, and AEs leading to premature discontinuation of study drug for the filgotinib 200 mg and filgotinib 100 mg treatment groups compared with their respective placebo groups across the subgroups by use of systemic corticosteroids or immunomodulators at maintenance baseline in Cohort 2. One death was reported among subjects with baseline use of systemic corticosteroids only and 1 death was reported among subjects with baseline use of immunomodulators only, both in the filgotinib 200 mg group.

Use in pregnancy and lactation

Pregnancy and lactation

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.

- For Study GS-US-418-3898, as of 31 March 2020 (study end date), a total of 4 subject pregnancies were reported: 1 subject in the filgotinib 100 mg group during induction, and 3 subjects (n = 1 filgotinib 100 mg, and n = 2 placebo following induction with filgotinib 100 mg) during maintenance. One partner pregnancy was reported in Study GS-US-418-3898.
- For Study GS-US-418-3899, as of 28 February 2020 (interim data cut-off date), no subject pregnancies were reported. A total of 4 partner pregnancies were reported in Study GS-US-418-3899.

A total of 2 filgotinib-exposed pregnancies and 5 partner pregnancies were reported from both studies. The outcome of these pregnancies in women exposed to filgotinib were:

- One elective termination without noted structural defects
- One ectopic pregnancy in the second subject, who underwent surgical termination via an urgent resection of right ovary and salpinx.

The outcome of pregnancies of partners to male study subjects were:

- Two healthy babies
- One baby with evidence of adverse effect
- One elective termination
- One unknown.

Fertility

No new information on the effects of filgotinib on fertility in nonclinical models was included in the submission.

Safety related to drug-drug interactions and other interactions

According to the MAH, no new findings relevant to the coadministration of filgotinib with other drugs were available.

Post marketing experience

According to the MAH, there have been no newly identified adverse reactions for filgotinib based on the post-marketing data available to date.

2.5.1. Discussion on clinical safety

Filgotinib was approved for treatment of adult patients with moderate to severe active rheumatoid arthritis in 2020 (EMEA/H/C/005113/0000). Important class effects of the JAK inhibitors include increased risk for infections (including herpes zoster), increased risk for venous thromboembolism, and concerns on an increased risk for gastrointestinal perforation, cardiovascular events and malignancy. JAK inhibitors are known to be teratogenic, and filgotinib is contraindicated during pregnancy.

For filgotinib specifically, there was concern that in animal studies, decreased fertility, impaired spermatogenesis and histopathological effects on male reproductive organs were observed. This had not been observed for other JAK inhibitors. At the CHMP's request at the time of the initial authorisation of the product, a stringent warning was included in section 4.4 of the SmPC to mitigate the risk regarding male fertility. In addition, adequate risk minimisation measures had been

implemented by the MAH. 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 [Study GS-US-418-4279] and MANTA-Ray [Study GLPG0634-CL-227] evaluating the impact on male fertility are expected to provide an understanding as to whether the findings are clinically relevant (see RMP sections). Interim data from these studies have recently been submitted and are being assessed by the CHMP in separate procedures (MEA007 and 008).

There were limited data in patients over 75 years of age and in patients with moderate renal impairment in the initial MAA. In the available data, an increased risk for serious AEs was observed for the 200 mg compared to the 100 mg dose. Therefore, a starting dose of 100 mg is recommended for RA patients aged 75 or above. A dose of 100 mg is also recommended in RA and UC patients with moderate or severe renal impairment.

In the current application, the safety analysis is based on 3 cohorts that pooled data from the pivotal phase 2b/3 study GS-US-418-3898 (cohort 1-induction study and cohort 2-maintenance study) and from the Phase 3 LTE Study GS-US-418-3899 (cohort 3-Long-term study).

Exposure

The mean treatment duration was 64.9 weeks for filgotinib 200 mg and 32.2 weeks for filgotinib 100 mg. A total of 621 patients were treated with filgotinib 200 mg >1 year, and a total of 141 patients were treated with filgotinib 100 mg >1 year. Overall, a total of 1253 subjects with UC have received at least 1 dose of filgotinib for a total of 1567.4 PY.

Adverse events

During the induction phase (both biologic-naïve and biologic-experienced patients), the exposure-adjusted incidence rate of treatment-emergent adverse events (TEAEs) was higher for filgotinib 200 mg (391.0 E/100PYs) than for filgotinib 100 mg (352.4 E/100PYs) but highest for placebo (422.1 E/100PYs). The EAIR of serious AEs and adverse events leading to discontinuation was lower for filgotinib 200 mg than for placebo.

Also during the maintenance phase, the incidence rate of TEAEs was slightly higher for filgotinib 200 mg (167.4 E/100PYs) than for filgotinib 100 mg (147.2 E/100PYs) and placebo (140.2 E/100PYs), but it is reassuring that TEAEs was less frequent in both filgotinib groups than in patients starting on filgotinib and later re-randomised to placebo during the maintenance phase. No dose-relation was observed for serious adverse events or AEs leading to discontinuation of study drug.

In induction study, biologic-naïve patients from cohort A the occurrence of TEAEs in filgotinib 200 mg arm and placebo are numerically similar (42%, and 41.6%, respectively) whereas in cohort B (biologic-experienced), TEAEs were increased in placebo arm (70.4%) compared to filgotinib 200mg (64.5%). Furthermore, in filgotinib 200 mg arm, overall TEAEs are more frequently reported in biologic-experienced patients compared to biologic-naïve patients as well as the number of AEs grade 3 or higher, serious AEs and TEAEs leading to premature discontinuation are also higher in cohort B than in cohort A.

In the overall data (induction and maintenance phases of GS-US-418-3898 and long-term extension study GS-US-418-3899), there was no dose-relation observed for the overall occurrence of adverse events, serious adverse events or adverse events leading to discontinuation. There were 5 deaths, all in the filgotinib 200 mg arm.

The most common adverse events were ulcerative colitis, nasopharyngitis, headache and upper respiratory tract infection. The incidence rates of nasopharyngitis, upper respiratory tract infection, and urinary tract infection were all higher in the filgotinib groups than in the placebo group.

There was one case of pulmonary embolism in the filgotinib 200 mg arm, and three cases of venous thrombosis in the placebo arm. Regarding arterial thrombosis, there were 3 cases reported in the filgotinib 200 mg arm (2 myocardial infarctions, 1 ischemic stroke), 1 case in the filgotinib 100 mg arm (1 TIA) and no cases in the placebo arm.

Deaths

There were 5 deaths, all in the filgotinib 200 mg arm.

- Subject A: No known risk factors for cardiovascular disease, who died on day 81 in the maintenance study. The autopsy showed severe arteriosclerosis and left ventricular failure.
- Subject B: Reported cause of death was asthma. Details on this case were requested by the CHMP, and it was confirmed that the patient had visited his general practitioner with clear signs of asthma.
- Subject C: No known risk factors for cardiovascular disease, who died from a myocardial infarction and ischemic stroke. The risk for arterial thrombosis is further discussed in the AESI section.
- Subject D: Died from COVID-19 infection, two years after starting treatment with filgotinib 200 mg. Although filgotinib does increase the risk for infections, firm conclusions on potential causality in this case with an ongoing pandemic cannot be determined.
- Subject E: Treated with open-label filgotinib 200 mg for approximately 1,5 years, who died from COVID-19 infection. Filgotinib had been discontinued around 1 month earlier due to endometrial cancer. Causality with filgotinib is less likely because treatment had been discontinued, although the exact timeframe is not clear.

In the recently presented pooled RA and UC data, the risk for death seems similar across all treatment groups (filgotinib 200 mg, filgotinib 100 mg, and placebo). Although there are no clear indications that filgotinib confers an increased risk for MACE *per se*, there is a small numerical imbalance in cardiovascular death. Hence, at the CHMP's request, the MAH has updated the section 4.4 of the SmPC and included a warning that Jyseleca should be used with caution in patients with cardiovascular risk factors.

Adverse events of special interest

Adverse events of interest included all infections; serious infections; herpes zoster infections; opportunistic infections; malignancy (excluding nonmelanoma skin cancer [NMSC]); NMSC; gastrointestinal (GI) perforations; and thromboembolic events (including venous thrombosis, pulmonary embolism (PE), arterial thrombosis, and cerebrovascular events).

The incidence rate of infections was higher for the filgotinib 200 mg group (69.5 E/100PYs) than for the filgotinib 100 mg (58.5 E/100PYs) and placebo (61.0 E/100PYs) groups. For serious infections, there was no dose-relation observed. For herpes zoster, there was a clearly higher risk for the filgotinib 200 mg group (22 cases, EAIR 1.8 E/100PYs) than for the filgotinib 100 mg and placebo groups (1 case each, EAIR 0.3E/100PYs). According to the MAH, most events were non-serious and were Grade 1 or 2 in severity. The risk for viral reactivation is included in the SmPC sections 4.4 and 4.8.

During the 10 week induction phase in the current study, the frequency of herpes zoster was 3/507 patients (0.6%) in the filgotinib 200 mg group and 0 cases in the placebo group. At the CHMP's

request, the MAH presented comparative data from the filgotinib RA and UC studies, where the risk for herpes zoster in the UC program was generally consistent with the RA population.

The exposure-adjusted incidence rate of malignancies was higher for both filgotinib doses (a total of 15 cases) than for placebo (0 cases). It is expected, however, that the treatment duration in the filgotinib arms are longer than for placebo. Of the 1161 patients included in the long-term extension study, a total of 871 were treated with filgotinib 200 mg; 157 with filgotinib 100 mg, and 133 with placebo. Since there is a latency for development of malignancies and the duration of treatment differs, comparison of the EAIRs must be made with caution. There was no specific pattern observed with regards to malignancies. As expected in the current patient population, there were cases of colon cancer/adenocarcinoma of the colon observed. The risk for malignancy will be further assessed through the GS-EU-418-5980 study, a non-interventional post-authorization safety study of filgotinib in the treatment of patients with moderately to severely active ulcerative colitis (category 3 in the RMP).

In cohort 1, three cases of NMSC were experienced, out of them two cases of basal cell carcinoma. One in the placebo group of the cohort A. The event was considered related to study drug and was unresolved as of the end of study. The second case was with filgotinib 200 mg in the cohort B. The event was considered not related to study drug and resolved. In cohort 3, seven cases of basal cell carcinoma were reported in filgotinib 200 mg (0.8%, EAER= 0.6/100 PYE). Six events were not related to filgotinib. The seventh case a non-serious basal cell carcinoma was considered related to filgotinib.

No GI perforation was reported.

Regarding venous thromboembolism, there is a warning in Section 4.4 of the SmPC because of a suspected class risk for the JAK inhibitors. In the UC studies, there was one case of pulmonary embolism in the filgotinib 200 mg arm, and three cases of venous thrombosis in the placebo arm. The CHMP considered that no update of the product information was warranted. However, a close monitoring of pulmonary embolism or clinical symptoms related to pulmonary embolism should be applied during the PSUR.

Regarding arterial thrombosis, there was an increased risk for both doses of filgotinib although the actual number of cases were few (n=3 in the filgotinib 200 mg arm and n=1 in the filgotinib 100 mg arm). The CHMP considered that no update of the product information was warranted.

In pooled data RA and UC data, the EAIR of MACE are numerically lower for filgotinib 200 mg (EAIR: 0.5E/100PYs) than for filgotinib 100 mg (EAIR: 0.6E/100PYs) and placebo (EAIR: 0.8E/100PYs), which is reassuring. In these data, there are no clear indications on an increased risk for MACE with filgotinib 200 mg. Although there are no clear indications that filgotinib confers an increased risk for MACE *per se*, there is a small numerical imbalance in cardiovascular death. See above warning on cardiovascular risk in Section 4.4 of the SmPC.

Laboratory findings

During induction, there was a slight increase in haemoglobin values in both filgotinib arms, probably reflecting response to therapy. Haemoglobin values were stable during the maintenance phase. Platelet counts decreased in all arms during induction with the largest decrease observed for the filgotinib arms, probably reflecting response to therapy. Neutrophil values decreased in both filgotinib arms during induction and was relatively stable during the maintenance phase. The risk for neutropenia is already included in sections 4.2, 4.4. and 4.8 of the SmPC.

Mean immunoglobulin values decreased in both filgotinib arms during induction and was relatively stable during maintenance. A slight increase was observed for the placebo arm. The risk for low immunoglobulin levels is not included in the SmPC. At the CHMP's request, the MAH presented details on IgA, IgG and IgM levels over time in the different cohorts of the UC study. The proportion of

patients with levels below lower limit of normal was small in all treatment groups and did not seem to be higher in the filgotinib 200 mg group than compared to the other treatment groups. The CHMP concluded that no SmPC update was needed.

Regarding liver-related parameters, in cohort A (biologic-naive patients), only AST > 3× ULN was observed in filgotinib 200 mg arm (0.8%) and no increased ALT or Alkalin phosphatase. Conversely in cohort B (biologic-experienced patients), one subject (0.4%) in the filgotinib 200 mg treatment group had ALT > 10 × ULN and 2 subjects (1.4%) in the placebo group had ALT > 5 × ULN.

Also, in cohort 2, AST and ALT > 10 × ULN abnormalities were reported in 1 subject (0.5%) of filgotinib 200 mg arm. No events were reported in the placebo group. ALT and ALT> 5 × ULN abnormalities were reported in 1 subject (0.5%) of filgotinib 200 mg. ALT and> 3 × ULN abnormalities were reported in 4 subjects (2.0%) and 2 subjects (1.0%) in filgotinib 200 mg arm respectively.

For grade 3 or 4 AST and ALT, the EAIRs in filgotinib 200 mg were 0.6/100 PYE and 1.5/100PYE in placebo.

In the long-term study, median ALT values across the treatment groups were generally stable. One patient in the filgotinib 100 mg group had AST > 20 × ULN (and ALT > 10 × ULN) on study day 506. This patient had normal baseline values.

CK and total cholesterol levels increased in both filgotinib arms, consistent with finding observed in the RA studies. LDL and HDL levels increased slightly, but the LDL/HDL ratios were generally unchanged. This is already adequately reflected in the SmPC. Serum creatinine increased in all treatment groups during induction but remained stable over the maintenance phase.

As regards hypophosphatemia, EAIR was 17.8/100 PYE in filgotinib 200 mg arm and 10.3/100 PYE in placebo. Considering that confounding factors may also explained the events of hypophosphataemia, no firm conclusion can be drawn. The CHMP considered that no update of the product information was warranted. However, the MAH should pursue the monitoring of this laboratory abnormalities as part of the PSUR.

Safety in special populations

Age, sex and race

During the induction phase, although the EAIR of TEAEs was higher for filgotinib 200 mg than for filgotinib 100 mg in patients aged 65 and above, it was not higher than for placebo and the risk for serious AEs and TEAEs leading to discontinuation was not higher for the filgotinib 200 mg dose. During the maintenance phase, AEs were more frequent among patients aged >65 years in all treatment groups. There were 2 deaths during the maintenance phase, both in patients aged >65 years treated with filgotinib 200 mg. During induction, the IR of infections was lower among patients aged >65 years than among the younger patients. During maintenance, the risk for infections did not seem to be dose-dependent among the elderly.

For rheumatoid arthritis, a starting dose of 100 mg is recommended for patients aged 75 years and above, whereas no dose adjustment was proposed for elderly patients with ulcerative colitis. This is considered acceptable to the CHMP. However, since there are no data available in UC patients >75 years, filgotinib is not recommended in patients aged 75 years and older. The SmPC section 4.2 has been updated accordingly.

The risk for AEs ad SAEs was numerically slightly higher for females than for males, but the difference is not considered to be clinically meaningful and a similar pattern was observed also for placebo.

There were no large differences in safety outcome between patients of different ethnicity.

Prior and concomitant medication

The incidence rate of overall adverse events appears higher in cohort of biologic-experienced patients than in patient without TNF-α or vedolizumab failure, notably for the SOC "infections and infestations", and this in both safety cohorts 1 and 2, and whatever filgotinib dosage. At the CHMP's request, the MAH provided a detailed analysis on the incidence rates of adverse events in cohort of biologic experienced patients compared to patients without TNF-α or vedolizumab failure, and notably for the SOC "infections and infestations", and whatever filgotinib dosage. Data show that in placebo arm this incidence rate is also high. Additionally, the MAH argued that the biologic-failure population typically represents patients with more severe disease activity and increased concomitant immunosuppressants use including systemic corticosteroids, all of which known as potential risk factors for infection. This CHMP considered that this could explain the observed difference between biologic-experienced patients and biologic-naïve patients.

The SmPCs for Xeljanz and Olumiant include information on the increased risk for herpes zoster in patients who are bDMARD-experienced. At the CHMP's request, the MAH presented data on the EAIR of herpes zoster in the respective treatment groups. In the data presented, there was a notable difference between biologic-naïve (7 cases, EAIR: 1.2E/100PYs) and biologic-experienced patients (15 cases, EAIR: 2.2E/100PYs), although it was agreed that the number of cases of herpes zoster in each group were quite few. The MAH argues that there is potential impact of concomitant medication; however it is noted that concomitant medication was given in a similar proportion of cases in both groups (3/8 patients in the biologic-naïve group and 7/16 patients in the biologic-experienced group) and thus there are no large differences between the groups. To further corroborate this issue, the MAH was asked to present data on the EAIR of herpes zoster in the respective treatment groups (bDMARD-naïve and bDMARD-experienced) in pooled data from the RA and UC studies. Based on these data, the CHMP considered that no SmPC updated were needed with regards to bDMARD-naïve and bDMARD-experienced patients. Considering that there seems to be a dose-dependent risk for herpes zoster, this issue is further pursued within the ongoing variation EMEA/H/C/005113/II/0008.

There was no evidence to suggest an increased EAIR for AEs for the filgotinib groups compared with the placebo group across the subgroups of patients with concomitant corticosteroids or immunosuppressants.

Pregnancy, lactation and male fertility

There was one case of elective termination in a pregnancy with a filgotinib-exposed father. Filgotinib is currently contraindicated during pregnancy and there's a warning about the potential risk of reduced fertility or infertility in male in Section 4.4 of the SmPC. There's also adequate information in Section 4.6 of the SmPC. As indicated above, the data from the ongoing clinical MANTA study [Study GS-US-418-4279] and MANTA-Ray [Study GLPG0634-CL-227] evaluating the impact on male fertility are being assessed by the CHMP in separate procedures (MEA 007 and MEA008).

2.5.2. Conclusions on clinical safety

The most common adverse events were ulcerative colitis, nasopharyngitis, headache and upper respiratory tract infection. The incidence rates of nasopharyngitis, upper respiratory tract infection, and urinary tract infection were all higher in the filgotinib groups than in the placebo group.

In the original UC application, there were 3 deaths reported in the UC clinical studies, all occurring in the filgotinib 200 mg group (2 cardiovascular, 1 asthma. EAIR of death=0.2E/100PYs). Two additional deaths in the filgotinib 200 mg group were reported in response to day 120 LoQ (COVID-19). The MAH presented pooled RA and UC data in which the risk for death seems similar across all treatment groups

(filgotinib 200 mg, filgotinib 100 mg, and placebo). Although there are no clear indications that filgotinib confers an increased risk for MACE per se, there is a small numerical imbalance in cardiovascular death. Hence, at the CHMP's request, the MAH has updated the section 4.4 of the SmPC with this information and included a warning that Jyseleca should be used with caution in patients at high cardiovascular risk.

In the overall safety dataset, there were 10 cases of malignancies (EAIR 0.8 E/100PYs) reported in the filgotinib 200 mg group, 5 cases (EAIR 1.3 E/100PYs), and no cases reported in the placebo group. The risk for malignancy will be further assessed through the GS-EU-418-5980 study, a non-interventional post authorization safety study of filgotinib in the treatment of patients with moderately to severely active ulcerative colitis (category 3 in the RMP).

Since there are no data are available in UC patients >75 years, filgotinib is not recommended in patients aged 75 years and older. The SmPC has been updated accordingly.

Overall, the CHMP concluded that the safety profile in the ulcerative colitis indication is consistent with the observed safety profile in the RA population and that the data provided supported the new indication in UC.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.0 with the following content:

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 count $<0.5 \times 10^9$ cells/L or an absolute neutrophil count $<1.0 \times 10^9$ cells/L. Recommendation in SmPC Section 4.4 on the management of infections in patients receiving filgotinib, and advice on patients at increased risk of infection. Recommendation in SmPC Section 4.4 to screen for tuberculosis (TB) and to initiate antimycobacterial therapy in patients with latent TB before administering filgotinib, and not to administer filgotinib to patients with active TB. The warning also recommends that patients are monitored for signs and symptoms of TB, including patients who tested negative for latent TB prior to initiating treatment. Section 4.4 also provides advice on the management of viral reactivation, including Herpes zoster and viral hepatitis. Recommendation in SmPC section 4.8 that a starting dose of 100 mg is administered to RA patients aged 75 years and older as there was a higher incidence of serious infections in this age group, although data are limited. Filgotinib is not recommended in patients with UC aged 75 years and older, as there is no data in this population. *Other routine risk minimization measures beyond the Product Information:* Medicine's legal status: restricted medical prescription to HCPs experienced in managing patients with RA or UC. *Additional risk minimization measures:* Healthcare professional guide, Patient Alert Card	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Serious and opportunistic infections adverse event follow-up form *Additional pharmacovigilance activities:* RA: GLPG0634-CL-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 UC: GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Ulcerative Colitis GS-EU-418-5980 Non-interventional Post-authorization Safety Study of Filgotinib in the Treatment of Patients with Moderately to Severely Active Ulcerative Colitis in Europe

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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 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 or UC. *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:* RA: 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 UC: GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Ulcerative Colitis GS-EU-418-5980 Non-interventional Post-authorization Safety Study of Filgotinib in the Treatment of Patients with Moderately to Severely Active Ulcerative Colitis in Europe
Important potential risk(s)		
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 or UC. *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
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:*	*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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Healthcare professional guide, Patient Alert Card	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 or UC.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Malignancy adverse event follow-up form *Additional pharmacovigilance activities:* RA: 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 UC: GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Ulcerative Colitis GS-EU-418-5980 Non-interventional Post-authorization Safety Study of Filgotinib in the Treatment of Patients with Moderately to Severely Active Ulcerative Colitis in Europe
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 or UC. *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:* RA: 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 UC: GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Ulcerative Colitis GS-EU-418-5980 Non-interventional Post-authorization Safety Study of Filgotinib in the Treatment of Patients with Moderately to Severely Active Ulcerative Colitis in Europe
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 or UC.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Gastrointestinal perforation adverse event follow-up form

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		Additional pharmacovigilance activities: RA: GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies 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 UC: GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Ulcerative Colitis GS-EU-418-5980 Non-interventional Post-authorization Safety Study of Filgotinib in the Treatment of Patients with Moderately to Severely Active Ulcerative Colitis in Europe
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 or UC.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Non-Melanoma Skin cancer adverse event follow-up form *Additional pharmacovigilance activities:* RA: GLPG0634-CL-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 UC: GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Ulcerative Colitis GS-EU-418-5980 Non-interventional Post-authorization Safety Study of Filgotinib in the Treatment of Patients with Moderately to Severely Active Ulcerative Colitis in Europe
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 or UC. *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:* RA: GLPG0634-CL-205 (DARWIN 3) long-term extension study in RA in subjects who received treatment in the parent studies

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		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 UC: GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Ulcerative Colitis GS-EU-418-5980 Non-interventional Post-authorization Safety Study of Filgotinib in the Treatment of Patients with Moderately to Severely Active Ulcerative Colitis in Europe
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 or UC.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Hyperlipidaemia adverse event follow-up form *Additional pharmacovigilance activities:* RA: 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 UC: GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Ulcerative Colitis GS-EU-418-5980 Non-interventional Post-authorization Safety Study of Filgotinib in the Treatment of Patients with Moderately to Severely Active Ulcerative Colitis in Europe

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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 or UC.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Varicella zoster virus (VZV) infection: Primary varicella (Chicken pox) or Herpes zoster (Shingles) follow-up form; *Additional pharmacovigilance activities:* RA: GLPG0634-CL-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 UC: GS-US-418-3899 (SELECTION LTE) A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Ulcerative Colitis GS-EU-418-5980 Non-interventional Post-authorization Safety Study of Filgotinib in the Treatment of Patients with Moderately to Severely Active Ulcerative Colitis in Europe
Missing information		
Use in patients with evidence of untreated chronic infection with hepatitis B or C	*Routine risk communication:* SmPC section 4.4 PL section 2	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Effect on vaccination efficacy	*Routine risk communication:* SmPC section 4.4 PL section 2 *Routine risk 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 with RA aged 75 years and above as clinical experience is limited, and that filgotinib is not recommended in patients with UC aged 75 years and older as there is no data in this population. Section 4.4 advises that as there is a higher incidence of serious infections in	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* RA: 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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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	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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to do minor updates to the Annex II and to implement minor editorial changes in the SmPC and Package Leaflet.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The addition of the ulcerative colitis indication to the currently approved PIL has not introduced significant changes to the text or layout.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disease that affects the colon, most commonly afflicting adults aged 30 to 40 years and resulting in disability. It is characterized by relapsing and remitting mucosal inflammation, starting in the rectum and extending to proximal segments of the colon. Although the incidence is stabilizing in Western countries, burden remains high, as prevalence exceeds 0.3%. The pathogenesis of UC is multifactorial and comprises immune, genetic, environmental, and microbial components. Hallmark symptoms of UC are bloody diarrhoea, rectal urgency, and tenesmus. The clinical course usually involves periods of remission interspersed with periods of active disease. Ulcerative colitis may also be associated with extraintestinal manifestations, including ocular lesions, skin lesions, arthritis, and primary sclerosing cholangitis. In addition, UC carries an increased risk of colorectal cancer.

3.1.2. Available therapies and unmet medical need

The treatment paradigm for UC has historically comprised an initial treatment for acute disease, with the goal of inducing a state of clinical remission, followed by a therapeutic intervention to maintain remission. Generally, patients presenting with mild to moderate disease activity are initially administered an anti-inflammatory agent such as a 5-aminosalicylate (5-ASA) derivative, with or without concurrent corticosteroids. Patients who fail to respond to initial therapy or who present with moderate to severe disease activity require treatment with more effective agents such as immunomodulators and biologic therapy. For nearly 2 decades, biological therapies were dominated by anti-tumour necrosis factor (TNF)-α agents but have recently included anti-integrin and anti–interleukin (IL)-12/IL-23 antibodies. Although biological therapies have led to substantial improvements in the care of patients with UC and have become an integral part of standard therapy, not all treated patients benefit from these therapies. As pointed out by the MAH, approximately one-third of patients do not respond after initiation of biological therapy (primary nonresponse) and among patients who initially respond to treatment with biologics, 30% to 50% eventually stop responding (secondary nonresponse). The clinical need for new therapies has led to the development of orally bioavailable small-molecule inhibitors that target signal transduction pathways involved in the pathogenesis of UC, including Janus kinase (JAK) inhibitors. Currently, there is only one JAK inhibitor approved for the treatment of UC (tofacitinib). There is an unmet medical need in these patients.

3.1.3. Main clinical studies

This application for approval of Jyseleca *"for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent"* is supported by data from one phase 2b/3 study, GS-US-418-3898 (SELECTION), which is a double-blind, randomised, placebo-controlled multi-center study that consists of two induction studies (Cohort A induction study and Cohort B induction study) and one randomised withdrawal maintenance study. In addition, supportive data from the ongoing Long-Term Extension Study GS-US-418 -3899 have been submitted.

Subjects in the study were adults with moderately to severely active ulcerative colitis (Mayo Clinic Score 6 to 12; endoscopy subscore ≥ 2; rectal bleeding subscore ≥ 1; stool frequency subscore ≥ 1; and Physician's Global Assessment subscore ≥ 2). Patients were permitted to use stable doses of concomitant therapies for ulcerative colitis, including oral aminosalicylates, oral corticosteroids, and immunomodulators (azathioprine, 6-MP, or methotrexate). In the Cohort A study, patients had to previously demonstrated an inadequate clinical response, loss of response to, or intolerance to at least one of the following agents: corticosteroids, oral azathioprine, 6-MP or MTX. In Cohort B study, patient had to previously demonstrated an inadequate clinical response, loss of response to, or intolerance to at least one TNF-α antagonist or vedolizumab.

In Cohort A induction study (Biologic naïve subjects) 660 subjects were randomized (245 patients received 200mg filgotinib, 278 patients received 100mg filgotinib and 137 patients received placebo). Overall, 618 subjects (93.8%) completed the cohort A introduction study. The main reasons for study drug discontinuation were subject decision and AEs, with a similar distribution between randomized groups.

In Cohort B induction study (biologic experienced subjects) 950 subjects were screened and 691 subjects were randomized (262 patients received 200mg filgotinib, 286 patients received 100mg filgotinib and 143 patients received placebo). Overall, 623 subjects (90.4%) completed the cohort B introduction study. The main reasons for study drug discontinuation were AEs and subject decisions, with a similar distribution between randomized groups.

Subjects who completed the induction studies and achieved either endoscopy/bleeding/stool frequency (EBS) remission or Mayo Clinic Score (MCS) response at Week 10 were rerandomized into the **Maintenance Study** (Week 11 to Week 58). Of the 1241 subjects who completed the induction studies, 664 subjects continued to the maintenance study. The 571 subjects treated with filgotinib in the induction phase were rerandomized in a 2:1 ratio to either continue on the assigned filgotinib regimen or switch to placebo. The 93 subjects who were treated with placebo in the induction phase continued with placebo treatment also during the maintenance phase. A total of 401 patients (60.4%) completed the maintenance phase, numerically more in the filgotinib/filgotinib 200 mg group (150/202, 74.3%) than in the filgotinib/filgotinib 100 mg group (104/179, 58.1%) and the placebo groups (filgotinib 200mg/placebo 41/99, 41.4%, filgotinib 100mg/placebo 42/91, 46.2% and placebo/placebo group 64/93, 68.8%. The main reason for discontinuation were disease worsening.

The study uses Endoscopic/Blood/Stool (EBS) remission as primary outcome, a combined endpoint derived from the Mayo clinical score, excluding the PGA. To reach EBS remission, the patient requires to have achieved an endoscopic response (a subscore of 0-1), cessation of rectal bleeding (subscore 0) and at least a 1-point decrease in stool frequency from baseline to achieve a subscore of 0 or 1. Although not fully consistent with the recommendations of the EMA guideline (CHMP/EWP/18463/2006 Rev.1 *Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis*) it is acceptable since it requires efficacy both in clinical and endoscopic outcomes.

3.2. Favourable effects

In the biologic naïve patients (Cohort A study), the primary endpoint, EBS remission at week 10, was achieved by 26.1% in the filgotinib 200 mg group, 19.1% in the filgotinib 100 mg group and 15.3% in the placebo group. Only the higher dose, filgotinib 200mg, was statistical significantly better than placebo (difference in proportions were 10.8% (95% CI: 2.1% to 19.5%, p = 0.0157)). The results from all the key secondary endpoints were in line with the results from the primary endpoint. It is noted that although only 12.2% achieved endoscopic remission (i.e. mayo endoscopic score 0), 33.9% achieved endoscopic response (score 0-1) an outcome that often are defined as mucosal healing (exploratory endpoint). In the placebo group the proportion were 3.6% for endoscopic remission and 20.4% for endoscopic response. Histologic remission was seen in 35% of patients in filgotinib 200mg group and 16% in the placebo group.

The proportions of patients achieving a MCS response at week 10 were 66.5% (163/245) in the filgotinib 200 mg group, 59.2% (164/277) in the filgotinib 100 mg group and 46.7% (64/137) in the placebo group and these patient were allowed to proceed into the maintenance study.

In the biologic experienced patients (Cohort B study), EBS remission at week 10 was achieved by 11.5% in the filgotinib 200 mg group, 9.5% in the filgotinib 100 mg group and 4.2% in the placebo group. Also, in this cohort, only the higher dose, filgotinib 200mg, was statistical significantly better than placebo (difference in proportion was 7.2% (CI 1.6% to 12.8%, p=0.013). None of the key secondary endpoints were statistically significant in this patient group, although it is noted that for histologic remission there was a numerically increase in favour for filgotinib 200 mg 19.8% vs 8.5% (difference 11.4% CI 4.2%, 18.6%). Only 3.4% and 17.2% of patients achieved endoscopic remission and endoscopic response. However, this patient group consisted of patients with a more severe disease, resistant to biologic therapies (50% of the patients had received both a TNF-inhibitor and vedolizumab) and more than half of the patients in the filgotinib 200 mg group (53.1%) achieved MCS response at week 10. In the filgotinib 100 mg and placebo group, 35.8% respectively 17.6% achieved MCS response at week 10. These patients were allowed to proceed to the maintenance study.

In the maintenance study, statistically significant treatment differences between filgotinib 200 mg and placebo at Week 58 were observed for the primary and all key secondary endpoints. The primary endpoint, EBS remission at week 58, was reached by 37.2% of the Filgotinib 200 mg group and 11.2% of the placebo group. Difference in proportion was 26.0% (95% CI 16.0% to 35.9%, p< 0.0001). The proportions of subjects who achieved 6-month corticosteroid-free EBS remission at Week 58 were 27.2% in the 200 mg group respective 6.4 % in the placebo group (difference in proportion 20.8% CI 7.7% to 33.9%). Treatment differences between filgotinib 100mg and respective placebo group were statistically significant for the primary endpoint (Filgotinib 100 mg: 23.8%, respective placebo: 13.5%; difference in proportions: 10.4%, 95% CI: −0.0% to 20.7%, p = 0.0420), but not for any of the key secondary endpoints at Week 58. In addition, 29.6% of the patients in the 100mg group discontinued the medication because of disease worsening.

In the 200 mg treated group, the proportion of bio-experienced patients achieving EBS remission at week 58 was 22/92 (23.9%) and the proportion of bio-naïve patients was 52/107 (48.6%).

These results are considered clinically relevant in the indication claimed by the MAH and supports the use of 200 mg QD dosing regimen.

3.3. Uncertainties and limitations about favourable effects

The primary endpoint, EBS remission, is a composite score. Ideally, co-primary endpoints on both symptomatic remission and endoscopic healing would have been utilised in line with the CHMP/EWP/18463/2006 rev 1 guideline. It is however noted that the chosen definition of remission did refer to all subscores of the Mayo score, excluding the physician global assessment subscore which is not of primary interest. So, it did encompass both symptomatic and endoscopic evaluation, and included assessment of cessation of rectal bleeding as requested by the guideline. As such the definition is acceptable. However, upon request, the MAH provided additional analysis exploring the components of the EBS remission endpoint separately. This analyse confirmed that in the overall population a beneficial effect was achieved in both the endoscopic and the symptomatic part of the EBS-score, both at week 10 and week 58.

There were some uncertainties regarding the clinical benefit for filgotinib in the bio-experienced patient group. Regarding induction of remission, the magnitude of difference in the primary endpoint, EBS remission, was small and filgotinib failed to reach statistical significance for all secondary endpoints in this cohort. In particular, there was a concern that the endpoint considered to be predictive for the long-term outcome/prognosis of the patients (endoscopic improvement/remission) was not achieved at a relevantly higher rate with filgotinib as compared to placebo. At the CHMP's request, the MAH provided additional information on this issue. When clinical and endoscopic response were analysed separately, a numerically better response could be seen also in the endoscopic part of the EBS-score and the additional information provided by the MAH regarding mucosal healing (defined as endoscopic respons in combination with histological remission), showing that a numerically greater proportion of biologic-experienced subjects achieved mucosal healing in the filgotinib 200 mg group compared with the placebo group at Week 58, added further evidence that a beneficial effect is seen also on the mucosa. In addition, the results achieved in the key secondary endpoints in the maintenance phase points towards a beneficial effect also regarding sustained efficacy and corticosteroid-free EBS-remission, although it is acknowledged that only a few patients achieved a complete healing of the mucosa.

Although statistically significant different from placebo, the proportion of subjects who achieved sustained EBS remission at Week 58 were low, only 18.1%. However, additional analysis provided

upon request showed that >60% of the patient in EBS-remission at week 10 were still in EBS remission at week 58.

Overall, there are support from secondary endpoints measuring different aspects of the disease.

In addition, since the study did not evaluate the effect of a higher induction dose followed by a lower maintenance dose, the MAH has agreed at the CHMP's request to conduct a study exploring a reduction of maintenance dose in a post-marketing setting.

3.4. Unfavourable effects

Important class effects of the JAK inhibitors include increased risk for infections (including herpes zoster), increased risk for venous thromboembolism, and concerns on an increased risk for gastrointestinal perforation, cardiovascular events and malignancy. JAK inhibitors are known to be teratogenic, and filgotinib is contraindicated during pregnancy.

For filgotinib specifically, there is concern that in animal studies, decreased fertility, impaired spermatogenesis and histopathological effects on male reproductive organs were observed. Therefore, the use of filgotinib should be restricted to female patients and male patients without intent of fathering a child. Two clinical studies (the MANTA studies) are currently ongoing aiming to further elucidate this issue. Interim data from these studies up to Week 26 are currently being assessed by the CHMP as part of separate procedures.

During the 11 week induction phase (both biologic-naïve and biologic-experienced patients) of study GS-US-418-3898, the exposure-adjusted incidence rate of treatment-emergent adverse events (TEAEs) was 391.0 E/100PYs for filgotinib 200 mg, 352.4 E/100PYs for filgotinib 100 mg and 422.1 E/100PYs for placebo. The EAIR of serious infections was 20.6 E/100PYs for filgotinib 200 mg, 23.8 E/100PYs for filgotinib 100 mg and 22.4 E/100PYs for placebo. There were no deaths in either treatment group.

Also, during the maintenance phase, the incidence rate of TEAEs was slightly higher for filgotinib 200 mg (167.4 E/100PYs) than for filgotinib 100 mg (147.2 E/100PYs) and placebo (140.2 E/100PYs). No dose-relation was observed for serious adverse events or AEs leading to discontinuation of study drug.

The most common adverse events were ulcerative colitis, nasopharyngitis, headache and upper respiratory tract infection. The incidence rates of nasopharyngitis, upper respiratory tract infection, and urinary tract infection were all higher in the filgotinib groups than in the placebo group.

Adverse events of interest included all infections; serious infections; herpes zoster infections; opportunistic infections; malignancy (excluding nonmelanoma skin cancer [NMSC]); NMSC; gastrointestinal (GI) perforations; and thromboembolic events (including venous thrombosis, pulmonary embolism (PE), arterial thrombosis, and cerebrovascular events).

The incidence rate of infections was 69.5 E/100PYs in the filgotinib 200 mg group, 58.5 E/100PYs in the filgotinib 100 mg group and 61.0 E/100PYs in the placebo group. For serious infections, there was no dose-relation observed. For herpes zoster, there were 22 cases (EAIR 1.8 E/100PYs) in the filgotinib 200 mg group and 1 case each (EAIR 0.3E/100PYs) in the filgotinib 100 mg and placebo groups.

Among laboratory parameters, during induction, there was a slight increase in haemoglobin values in both filgotinib arms. Haemoglobin values were stable during the maintenance phase. Platelet counts decreased in all arms during induction with the largest decrease observed for the filgotinib arms. Neutrophil values decreased in both filgotinib arms during induction and was relatively stable during the maintenance phase. Mean immunoglobulin values decreased in both filgotinib arms during induction and was relatively stable during maintenance. A small increase in ALT levels was observed in

all treatment groups during induction, but values were relatively stable during maintenance. Increases in AST levels was more prominent in the filgotinib groups. CK and total cholesterol levels increased in both filgotinib arms. The CHMP considered that this information was already adequately addressed in the SmPC and that no updates were warrented.

AEs were more frequent among patients aged >65 years in all treatment groups. For rheumatoid arthritis, a starting dose of 100 mg is recommended for patients aged 75 years and above, whereas no dose adjustment was proposed for elderly patients with ulcerative colitis. This is considered acceptable to the CHMP. However, since there are no data are available in UC patients >75 years, filgotinib is not recommended in patients aged 75 years and older. The SmPC has been updated accordingly.

3.5. Uncertainties and limitations about unfavourable effects

Important uncertainties pertain to adverse events of low frequency and long latency, for example cardiovascular disease and malignancy.

At the approval of filgotinib for treatment of patients with RA there was concern on the risk for impaired male fertility based on preclinical findings. Two clinical studies (the MANTA studies) are currently ongoing aiming to further elucidate this issue. Interim data from these studies up to Week 26 has recently been submitted within MEA 007 and MEA 008. The results will be thoroughly assessed within the MEA procedures, and the issue is not further pursued within this variation.

In the original UC application, there were 3 deaths reported in the UC clinical studies, all occurring in the filgotinib 200 mg group (2 cardiovascular, 1 asthma. EAIR of death=0.2E/100PYs). Two additional deaths in the filgotinib 200 mg group were reported in response to day 120 LoQ (COVID-19). The MAH presented pooled RA and UC data in which the risk for death seems similar across all treatment groups (filgotinib 200 mg, filgotinib 100 mg, and placebo). Although there are no clear indications that filgotinib confers an increased risk for MACE per se, there is a small numerical imbalance in cardiovascular death. Hence, at the CHMP's request, the MAH has updated the section 4.4 of the SmPC with this information and included a warning that Jyseleca should be used with caution in patients at high cardiovascular risk.

There was one case of pulmonary embolism in the filgotinib 200 mg arm, and three cases of venous thrombosis in the placebo arm. Regarding arterial thrombosis, there were 3 cases reported in the filgotinib 200 mg arm (2 myocardial infarctions, 1 ischemic stroke), 1 case in the filgotinib 100 mg arm (1 TIA) and no cases in the placebo arm. The CHMP considered that no update of the existing warning in Section 4.4 was warranted. However, a close monitoring of pulmonary embolism or clinical symptoms related to pulmonary embolism should be applied during the PSUR.

In the overall safety dataset, there were 10 cases of malignancies (EAIR 0.8 E/100PYs) reported in the filgotinib 200 mg group, 5 cases (EAIR 1.3 E/100PYs), and no cases reported in the placebo group. The risk for malignancy will be further assessed through the GS-EU-418-5980 study, a non-interventional post authorization safety study of filgotinib in the treatment of patients with moderately to severely active ulcerative colitis (category 3 in the RMP).

In induction study, biologic-naïve patients from cohort A the occurrence of TEAEs in filgotinib 200 mg arm and placebo are numerically similar (42%, and 41.6%, respectively) whereas in cohort B (biologic-experienced), TEAEs were increased in placebo arm (70.4%) compared to filgotinib 200mg (64.5%). Furthermore, in filgotinib 200 mg arm, overall TEAEs are more frequently reported in biologic-experienced patients compared to biologic-naïve patients as well as the number of AEs grade 3 or higher, serious AEs and TEAEs leading to premature discontinuation are also higher in cohort B than in cohort A. At the CHMP's request, the MAH provided a detailed analysis on the incidence rates of

adverse events in cohort of biologic experienced patients compared to patients without TNF-α or vedolizumab failure, and notably for the SOC "infections and infestations", irrespective of filgotinib dosage. Data show that in placebo arm this incidence rate is also high. Additionally, the MAH argued that the biologic-failure population typically represents patients with more severe disease activity and increased concomitant immunosuppressants use including systemic corticosteroids, all of which known as potential risk factors for infection. Thus CHMP considered that this could explain the observed difference between biologic-experienced patients and biologic-naïve patients.

3.6. Effects Table

Table 61 Effects Table for Jyseleca and Ulcerative Colitis (data cut-off: 28 February 2020)

Effect	Short description	Unit	Filgotinib	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
EBS remission at week 10-	Induction Phase bio-naïve patients	N (%)	200 mg 64/245 (26.1) 100 mg 53/277 (19.1)	21/137 (15.3)	P=0.0157 P=0.3379	GS-US-418-3898
EBS remission at week 10	Induction Phase bio-experienced patients	N (%)	200 mg 30/262 (11.5) 100 mg 27/285 (9.5)	6/142 (4.2)	P=0.013 P=0.0645	GS-US-418-3898
EBS remission at week 58	Maintenance phase	N (%)	200 mg 74/199 (37.2) 100 mg 41/172 (23.8)	11/98 (11.2) 12/89 (13.5)	P<0.0001 P=0.0420	GS-US-418-3898
Unfavourable Effects						
TEAEs	Induction phase	N (E/100 PYs)	271/507 (391.0)	156/279 (422.1)		GS-US-418-3898
TEAEs	Maintenance phase	N (E/100 PYs)	134/202 (167.4)	57/93 (140.2)		GS-US-418-3898
TEAEs	Overall safety dataset	N (E/100 PYs)	3280/971 (265.8)	1004/469(309.2)		GS-US-418-3898/99
SAEs	Induction phase	N (E/100 PYs)	22/507 (20.6)	13/279 (22.4)		GS-US-418-3898
SAEs	Maintenance phase	N (E/100 PYs)	9/202 (5.9)	4/93 (5.9)		GS-US-418-3898
SAEs	Overall safety dataset	N (E/100 PYs)	147/971 (11.9)	40/469 (12.3)		GS-US-418-3898/99
Deaths	Overall safety dataset	N (E/100 PYs)	3 (0.2)	0		GS-US-418-3898/99
Serious infections	Overall safety dataset	N (E/100 PYs)	27/971 (2.2)	7/469 (2.2)		GS-US-418-3898/99

Abbreviations: TEAE=treatment-emergent adverse event, SAE=serious adverse event

Notes: "Treatment" refers to filgotinib 200 mg (dose proposed to be marketed), "Control" to placebo.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A statistically significant and clinically relevant effect as measured by EBS remission has been demonstrated for Jyseleca 200 mg, both as induction and maintenance treatment, in the population of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

For patients with previous biological therapy, the treatment effect was modest, and none of the secondary endpoints in the induction phase reached statistically significance. It is acknowledged that this patient group consisted of patients with a more severe disease, resistant to biologic therapies, and although the clinical relevance of the modest efficacy seen in this patient group was questioned, especially regarding the endpoints considered to be predictive for the long-term outcome/prognosis of the patients (i.e. endoscopic improvement/remission), the MAH provided additional analysis on sustained long term efficacy, corticosteroid-free remission and mucosal healing (endoscopic response/histologic remission) confirms a beneficial effect also in this subpopulation.

The data submitted supports the proposed posology of 200 mg once daily for induction and maintenance therapy.

Overall, there are support from secondary endpoints measuring different aspects of the disease.

From a safety perspective, the safety profile seems overall consistent with the safety profile observed in the RA indication. Important class effects of the JAK inhibitors include increased risk for infections (including herpes zoster), increased risk for venous thromboembolism, and concerns on an increased risk for gastrointestinal perforation, cardiovascular events and malignancy. JAK inhibitors are known to be teratogenic, and filgotinib is contraindicated during pregnancy. For filgotinib specifically, there is concern that in animal studies, decreased fertility, impaired spermatogenesis and histopathological effects on male reproductive organs were observed. Therefore, the use of filgotinib should be restricted to female patients and male patients without intent of fathering a child. Two clinical studies (the MANTA studies) are currently ongoing aiming to further elucidate this issue. Interim data from these studies up to Week 26 are currently being assessed by the CHMP as part of separate procedures.

At the approval of the RA indication, there was concern that the exposure-adjusted incidence rate of death was higher for filgotinib 200 mg than for the comparator adalimumab, although the actual numbers were small. The relevance of this observation was considered difficult to assess taken into account that overall the differences between the groups were small with overlapping 95% CIs. Furthermore, there were no dose-dependency observed for the most important AESIs of serious infections, MACE or malignancy. Also in the UC population, there is a numerically higher incidence of death in the filgotinib 200 mg group than in the filgotinib 100 mg and placebo groups but again, the total number of cases are few. In the pooled data presented during this procedure, the risk for death seems similar across all treatment groups (filgotinib 200 mg, filgotinib 100 mg, and placebo). Although there are no clear indications that filgotinib confers an increased risk for MACE *per se*, there is a small numerical imbalance in cardiovascular death. Hence, at the CHMP's request, the MAH has strengthen the warning in Section 4.4 of the SmPC to further minimise the risk in patients at high risk for cardiovascular disease.

In the overall safety dataset, there were 10 cases of malignancies (EAIR 0.8 E/100PYs) reported in the filgotinib 200 mg group, 5 cases (EAIR 1.3 E/100PYs), and no cases reported in the placebo group. The risk for malignancy will be further assessed through the GS-EU-418-5980 study, a non interventional

post authorization safety study of filgotinib in the treatment of patients with moderately to severely active ulcerative colitis (category 3 in the RMP).

Since there are no data are available in UC patients >75 years, filgotinib is not recommended in patients aged 75 years and older.

3.7.2. Balance of benefits and risks

The CHMP considered that the suggested indication text "Jyseleca is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent" adequately reflects the intended population.

The study did not evaluate the effect of a higher induction dose followed by a lower maintenance dose. Hence, at the CHMP's request, the MAH accepted to conduct a study exploring a reduction of maintenance dose in a post-marketing setting.

3.8. Conclusions

The overall B/R of Jyseleca in the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the treatment of active ulcerative colitis in adults patients for Jyseleca. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC and the Package Leaflet are updated accordingly. The RMP is updated to Version 4.0. In addition, the Marketing authorisation holder (MAH) took the opportunity to do minor updates to the Annex II and to implement minor editorial changes in the SmPC and Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Jyseleca-H-C-005113-II-0001'

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted)