Report on the Deliberation Results

September 8, 2020

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Jyseleca Tablets 100 mg
	Jyseleca Tablets 200 mg
Non-proprietary Name	Filgotinib Maleate (JAN*)
Applicant	Gilead Sciences K.K.
Date of Application	October 8, 2019

Results of Deliberation

In its meeting held on September 4, 2020, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, and the re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specific number of patients have been collected, in order to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

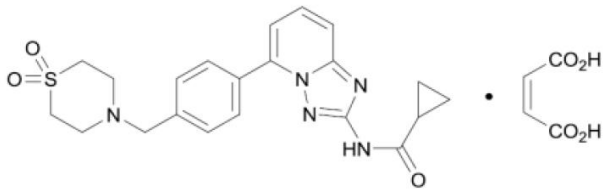
**Japanese Accepted Name (modified INN)*

Review Report

August 26, 2020
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Jyseleca Tablets 100 mg Jyseleca Tablets 200 mg
Non-proprietary Name	Filgotinib Maleate
Applicant	Gilead Sciences K.K.
Date of Application	October 8, 2019
Dosage Form/Strength	Tablets, each containing 127.24 mg or 254.48 mg of filgotinib maleate (equivalent to filgotinib 100 mg or 200 mg, respectively)
Application Classification	Prescription drug, (1) Drugs with a new active ingredient
Chemical Structure	



Molecular formula: $C_{21}H_{23}N_5O_3S \cdot C_4H_4O_4$

Molecular weight: 541.58

Chemical name: *N*-(5-{4-[(1.1-Dioxo-λ^6-thiomorpholin-4-yl)methyl]phenyl}[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)cyclopropanecarboxamide monomaleate

Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of rheumatoid arthritis in patients who have had an inadequate response to conventional therapies (including the prevention of structural joint damage) and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. The applicant needs to take sufficient safety measures, as in the case of other conventional Janus kinase (JAK) inhibitors used in patients with rheumatoid arthritis, because serious adverse reactions such as serious infections and malignancies may occur following the clinical use of the product. Post-marketing surveillance, covering all patients treated with the product, should be conducted for early identification of the safety profile until data from a specific number of patients have been collected. The applicant further needs to conduct investigations to follow-up the onset of serious infections, malignant tumors, etc. in patients receiving long-term treatment with the product.

Indication	Rheumatoid arthritis in patients who have had an inadequate response to conventional therapies (including the prevention of structural joint damage)
Dosage and Administration	The usual adult dosage is 200 mg of filgotinib orally once daily. The dose may be adjusted to 100 mg once daily according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specific number of patients have been collected, in order to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

Attachment

Review Report (1)

August 13, 2020

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Jyseleca Tablets 100 mg Jyseleca Tablets 200 mg
Non-proprietary Name	Filgotinib Maleate
Applicant	Gilead Sciences K.K.
Date of Application	October 8, 2019
Dosage Form/Strength	Tablets, each containing 127.24 mg or 254.48 mg of filgotinib maleate (equivalent to filgotinib 100 mg or 200 mg, respectively)
Proposed Indication	Rheumatoid arthritis (including the prevention of structural joint damage)
Proposed Dosage and Administration	The usual adult dosage is 200 mg of filgotinib orally once daily. The dose may be adjusted to 100 mg once daily according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Filgotinib maleate, the active ingredient of Jyseleca Tablets 100 mg and 200 mg, is a Janus kinase (JAK) inhibitor discovered by Galapagos NV, and co-developed by Galapagos NV and Gilead Sciences, Inc. (the US).

Rheumatoid arthritis (RA) is a disease characterized by chronic inflammation of the joints and affects 0.7 to 1.2 million people in Japan (*Mod Rheumatol.* 2014;24:33-40). Inflammatory responses in the synovial tissue cause joint swelling, pain, stiffness, and restricted mobility, and may lead to irreversible joint damage. The treatment guidelines issued in Japan, the US, and Europe recommend treat-to-target (T2T) strategies, which aim at achieving clinical remission or low disease activity as soon as possible upon diagnosis (*Guidelines for the Management of Rheumatoid Arthritis*, issued by Japan College of Rheumatology 2014 [JCR RA Treatment Guidelines 2014], *Arthritis Care Res.* 2016;68:1-25, *Ann Rheum Dis.* 2017;76:960-77). The pharmacotherapy of RA involves methotrexate (MTX) and other conventional disease modifying anti-rheumatic drugs (cDMARDs) as the first-line treatment options. The use of biological products such as tumor necrosis factor (TNF)-α inhibitors is recommended for patients who had an inadequate response to cDMARDs. In recent years, the recommendation has been expanded to include JAK inhibitors as treatment options (*Ann Rheum Dis.* 2017;76:960-77). In Japan, JAK inhibitors, namely, tofacitinib (2013), baricitinib (2017), peficitinib (2019), and upadacitinib (2020), were approved for the treatment of patients with RA with an inadequate response to conventional therapies.

The clinical development of Jyseleca was initiated in [redacted] 20[redacted] outside Japan, and in [redacted] 20[redacted] in Japan. The marketing application for Jyseleca was filed with the findings from studies including the global studies conducted in many regions including Japan.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to pale yellow-white solid. The general properties of the drug substance, including description, solubility, hygroscopicity, melting point, dissociation constant, distribution coefficient, crystal form (single crystal X-ray structure), and thermal analysis (differential scanning calorimetry) have been determined.

Its chemical structure has been elucidated by proton and carbon nuclear magnetic resonance spectroscopy (^{1}H- and ^{13}C-NMR), mass spectrometry, elemental analysis, infrared absorption spectroscopy (IR), ultraviolet-visible spectroscopy (UV-VIS), single crystal X-ray structure analysis, and powder X-ray diffraction.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted], [redacted], [redacted], and [redacted] as the starting materials.

A quality-by-design (QbD) approach has been applied to the following to formulate the quality control strategy (Table 1).

- Identification of critical quality attributes
- Identification of critical process parameters based on the quality risk assessment and [redacted] analysis

Table 1. Outline of the control strategy for the drug substance

Critical quality attributes	Control method
[redacted], Impurity A, [redacted], Impurity [redacted], and Impurity B	Manufacturing process, [redacted]
Impurity C, Impurity D (Impurity D1, Impurity D2), Impurity E, [redacted], and [redacted]	Manufacturing process

The [redacted] process has been defined as the critical process step.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR and high performance liquid chromatography [HPLC]), purity (appearance of solution, related substances [HPLC], residual solvents, and Impurity B (gas chromatography [GC])), water content, [redacted], [redacted] ([redacted]) and assay (HPLC).

2.1.4 Stability of drug substance

Table 2 summarizes the primary stability studies on the drug substance. The results showed that the drug substance is stable. The results of a photostability study also show that the drug substance is photostable.

Table 2. Stability studies on the drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	4 pilot batches	30°C	75%RH	Polyethylene bag (double-layer) + [redacted] aluminum foil bag + high-density polyethylene drum	24 months
Accelerated	4 pilot batches	40°C	75%RH		6 months

The above results have proposed a retest period of 36 months for the drug substance when placed in a double-layered polyethylene bag, [redacted] in aluminum foil bag, stored in a high density polyethylene drum at room temperature in accordance with the "Guidelines on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004, dated June 3, 2003). The long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet containing 127.24 mg or 254.48 mg of the drug substance (equivalent to filgotinib 100 mg or 200 mg, respectively). The excipients used are microcrystalline cellulose, lactose hydrate, pregelatinized starch, fumaric acid, magnesium stearate, light anhydrous silicic acid, and Opadry II beige [redacted].

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of blending, [redacted] granulation, tableting, film-coating, and packaging and labeling steps. The [redacted] process has been defined as the critical process step, and process control items and values have been established for [redacted], [redacted], and [redacted] steps.

A QbD approach has been applied to the following to formulate the quality control strategy (Table 3).

- Identification of critical quality attributes
- Identification of critical process parameters based on the quality risk assessment

Table 3. Outline of the control strategy for the drug product

Critical quality attributes	Control method
[redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]	Manufacturing process, [redacted]
[redacted]	Manufacturing process

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description (appearance), identification (HPLC and UV-VIS), purity (related substances [HPLC]), water content, uniformity of dosage units (mass variation test), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Table 4 summarizes the primary stability studies on the drug product. The results showed that the drug product is stable. The results of a photostability study also show that the drug product is photostable.

Table 4. Stability studies on the drug product

Study	Formulation	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	100-mg tablet	3 pilot batches	30°C	75%RH	Blister pack + aluminum bag with desiccant	18 months
	200-mg tablet	3 commercial-scale batches				
Accelerated	100-mg tablet	3 pilot batches	40°C	75%RH		6 months
	200-mg tablet	3 commercial-scale batches				

The above results have proposed a shelf life of 24 months for the drug product when packaged in a blister pack (polychlorotrifluoroethylene/polyvinyl chloride film/aluminum foil) and then put in an aluminum bag (consisting of polyethylene terephthalate, polyethylene, aluminum foil, and polyethylene layers) with desiccant at room temperature in accordance with the "Guidelines on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004, dated June 3, 2003). The long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Following study results were submitted as the nonclinical pharmacological data: Primary pharmacodynamics that include investigation on inhibition of JAK family kinases, effects on signal transducer and activator of transcription (STAT) protein phosphorylation and other reactions, and effects in collagen-induced arthritis

(CIA) rat models; Secondary pharmacodynamics that include investigation of effects on kinases, non-kinase enzymes, and receptors; and Safety pharmacology that include investigation of effects on the central nervous, cardiovascular, and respiratory systems.

Pharmacological parameters are expressed as the mean.

3.1 Primary pharmacodynamics

3.1.1 Inhibition of JAK family kinases (CTD 4.2.1.1.1, 4.2.1.1.2, 4.2.1.1.12, 4.2.1.1.13, 4.2.1.1.16, and 4.2.1.1.20)

Assays were performed using recombinant human JAKs 1, 2, 3, and tyrosine kinase 2 (TYK2). Table 5 shows the IC_{50} of filgotinib and its major metabolite GS-829845 against JAKs 1, 2, 3, and TYK2 [see Section 4.3].

Table 5. The inhibitory activity of filgotinib and GS-829845 against recombinant human JAK family kinases (IC_{50}, nmol/L)

	Filgotinib			GS-829845
	FRET[a)]	TR-FRET[b)]	^{33}P incorporation[c)]	^{33}P incorporation[c)]
JAK1	10	16	53	546
JAK2	28	70	69	624
JAK3	810	Not studied	311	>3,606
TYK2	116	Not studied	177	>2,996

a) in the presence of 10 µmol/L ATP; b) in the presence of 3.5 (JAK1) or 3.75 (JAK2) µmol/L ATP; c) in the presence of 0.72 (JAK1), 0.36 (JAK2 and JAK3), or 0.036 (TYK2) µmol/L unlabeled ATP

3.1.2 Effects on phosphorylation of STAT proteins and other reactions

3.1.2.1 Investigation using cell lines (CTD 4.2.1.1.3, 4.2.1.1.14, and 4.2.1.1.20)

Table 6 shows the IC_{50} of filgotinib and GS-829845 against STAT phosphorylation in different types of cell lines.

Table 6. The inhibitory activity of filgotinib and GS-829845 against STAT phosphorylation in different types of cell lines

Cell line	Stimulation	Phosphorylation of STAT protein studied	JAK involved	IC_{50} (nmol/L)	
				Filgotinib	GS-829845
HeLa	OSM	STAT1	JAK1/JAK2	1,045	>7,428
THP-1	IL-4	STAT6	JAK1/JAK3	179	Not studied
NK-92	IL-2	STAT5	JAK1/JAK3	424	
TF1	IL-3	STAT5	JAK2	3,524	
UT-7-EPO	EPO	STAT5	JAK2	>10,000	
U2OS	IFNαB2	STAT1	JAK2/TYK2	465	
U2OS	IFNγ	STAT1	JAK1/JAK2	3,364	

Stimuli conditions: oncostatin M (OSM) (33 ng/mL); interleukin (IL)-4 (10 ng/mL); IL-2 (1 ng/mL); IL-3 (30 ng/mL); erythropoietin (EPO) (1 U/mL); interferon (IFN)αB2 (30,000 U/mL); and IFNγ (20 ng/mL)

3.1.2.2 Whole blood studies (CTD 4.2.1.1.10, 4.2.1.1.11, 4.2.1.1.18, 4.2.1.1.20, 4.2.1.1.21, 4.2.1.1.22, and 4.2.1.1.25)

Inhibition of STAT phosphorylation and interferon (IFN) production was studied in human and rodent whole blood assays. Table 7 and Table 8 show IC_{50} of filgotinib and GS-829845.

Table 7. The inhibitory activity of filgotinib and GS-829845 against STAT phosphorylation and IFNγ production in human whole blood

Stimulation	Reaction studied	JAK involved	IC_{50} (nmol/L)	
			Filgotinib	GS-829845
IL-6	STAT1 phosphorylation	JAK1	629-1,180	11,850-11,917
IL-2	STAT5 phosphorylation	JAK1/JAK3	1,789	19,626
IFNα	STAT1 phosphorylation	JAK1/TYK2	506-1,127	15,423
IL-6	STAT3 phosphorylation	JAK1/JAK3/TYK2	2,632-3,410	28,860
IL-2	IFNγ production	JAK1/JAK3	316	Not studied
GM-CSF	STAT5 phosphorylation	JAK2	17,453	>100,000
TPO	STAT3 phosphorylation	JAK2	7,118	Not studied

Stimuli conditions: IL-6 (10, 30, or 750 ng/mL); IL-2 (4 or 10 ng/mL); IFNα (5 ng/mL or 1,000 U/mL); GM-CSF (20 pg/mL); thrombopoietin (TPO) (30 ng/mL)

Table 8. The inhibitory activity of filgotinib and GS-829845 against STAT phosphorylation in human or rodent whole blood

Reaction studied	JAK involved	Animal species (whole blood and IL-6)	IL-6 stimulation	IC_{50} (μmol/L)	
				Filgotinib	GS-829845
STAT1 phosphorylation	JAK1	Human	30 ng/mL	1.18	11.85
		Rat	200 ng/mL	1.57	10.83
		Mouse	10 ng/mL	3.10	19.9
STAT3 phosphorylation	JAK1/JAK3/TYK2	Human	30 ng/mL	3.41	28.86
		Rat	200 ng/mL	4.43	25.93
		Mouse	10 ng/mL	10.27	74.95

3.1.3 Effects on CIA rat models (CTD 4.2.1.1.9, 4.2.1.1.15, and 4.2.1.1.19)

Bovine type II collagen was administered to female rats twice (Days 1 and 10) to induce arthritis. A 2-week treatment with filgotinib 0 (vehicle), 0.1, 0.3, 1, 3, 10, or 30 mg/kg orally once daily resulted in a dose-dependent suppression of paw edema at ≥0.3 mg/kg, and a dose-dependent decrease in clinical score[1)] at ≥0.1 mg/kg. The radiological imaging assessment of the hindlimb indicated an inhibition of bone erosion at ≥10 mg/kg and a decrease of Larsen score[2)] at ≥3 mg/kg.

Following administration of GS-829845 0 (vehicle), 2, 10, or 50 mg/kg orally once daily for 2 weeks to CIA rat models, no effects were observed on paw edema or inflammation in the limbs.

Bovine type II collagen was administered to female rats twice (Days 1 and 7) to induce arthritis, which is followed by a 13-day once-daily oral treatment with vehicle, filgotinib 3 mg/kg alone, GS-829845 25 mg/kg alone, or a combination of filgotinib/GS-829845 (3 and 25 mg/kg, respectively). While the AUC[3)] of the ankle joint diameter was not affected by treatment with filgotinib 3 mg/kg alone, the ankle joint diameter decreased in rats treated with GS-829845 25 mg/kg alone and with a combination of filgotinib/GS-829845 (3 and 25 mg/kg, respectively). Compared with vehicle, the inhibition of ankle joint swelling by filgotinib 3 mg/kg alone, by GS-829845 25 mg/kg alone, and by the combination of filgotinib/GS-829845 (3 and 25 mg/kg, respectively) was 7%, 28%, and 54%, respectively.

[1)] In this scoring system, inflammation in the limbs was assessed on a scale of 0 (no symptom) to 4 (maximum inflammation) and summed (maximum possible score of 16 points)
[2)] In this scoring system, bone erosion was assessed on a scale of 0 (normal) to 5 (bony outlines are not identifiable)
[3)] Area under the drug concentration-time curve of ankle joint diameter up to Day 14

3.2 Secondary pharmacodynamics

3.2.1 Effects on enzymes and receptors (CTD 4.2.1.2.1, 4.2.1.2.2, 4.2.1.2.3, 4.2.1.2.8, 4.2.1.2.11, and 4.2.1.2.12)

The effects of filgotinib on 451 kinases, 70 receptors, and 22 non-kinase enzymes were studied. At clinically relevant concentrations, ≥50% inhibition was expected for the following enzymes in addition to JAK1 kinase: Aurora B, FLT1, FLT3, FLT4, FMS, MER, and PPARγ. The inhibitory effects of filgotinib on these 7 enzymes were studied using cells. When concentrations up to 10 μmol/L filgotinib were tested, inhibition was observed only for FLT4, with an IC_{50} of 6.9 μmol/L.

No meaningful inhibitory effects of GS-829845 were observed for kinases and receptors at concentrations up to 30 μmol/L.

3.3 Safety pharmacology

Table 9 shows the results of safety pharmacology studies of filgotinib and GS-829845.

Table 9. Summary of the safety pharmacology studies

Organ system	Test system	Test parameter/ method	Dose	Route of administration	Finding	CTD
Central nervous system	SD rat (6 males/group)	Irwin test (without anesthesia)	Filgotinib 20, 60, 180 mg/kg	Oral	No effect	4.2.1.3.1
	SD rat (8 males/group)		GS-829845 40, 100, 180 mg/kg			4.2.1.3.8
Cardiovascular system	hERG-transfected HEK293 cells	hERG current	Filgotinib 10, 30 μmol/L	*In vitro*	10 μmol/L, 14.3% inhibition 30 μmol/L, 15.7% inhibition	4.2.1.3.4
			GS-829845 10, 30 μmol/L		10 μmol/L, 14.2% inhibition 30 μmol/L, 19.2% inhibition	4.2.1.3.6
	Beagle dog (3/sex/group)	Blood pressure, electrocardiogram, heart rate (without anesthesia)	Filgotinib 10, 30, 100 mg/kg	Oral	No effect	4.2.1.3.3
			GS-829845 25, 50, 100 mg/kg		50 mg/kg, heart rate increased by 7-28 bpm 100 mg/kg, heart rate increased by 41-52 bpm blood pressure decreased by approximately 25 mmHg	4.2.1.3.5
Respiratory system	SD rat (8 males/group)	Respiratory function (without anesthesia)	Filgotinib 20, 60, 180 mg/kg	Oral	No effect	4.2.1.3.2
			GS-829845 40, 100, 180 mg/kg			4.2.1.3.7

3.R Outline of the review conducted by PMDA

The applicant's explanation about the mechanism of action of filgotinib in patients with RA:

JAK1 is an essential mediator of the signaling pathways downstream of multiple cytokines, growth factors, and chemokine receptors involved in innate and adaptive immune responses. Inhibition of JAK1 blocks signal transduction mediated by proinflammatory cytokines such as IL-6, thereby suppressing the activation and proliferation of lymphocytes involved in the pathogenesis of RA (*EMBO J.* 1995;14:1421-9). Because data from non-clinical pharmacology studies demonstrated that filgotinib is primarily a selective inhibitor of JAK1, it was expected to be effective in the treatment of RA. While GS-829845, the major metabolite of filgotinib, also exhibits JAK selectivity, the IC_{50} for inhibition of JAK1 was approximately 10-fold compared with that of filgotinib. In humans, however, following administration of filgotinib, the exposure of GS-829845 was

higher ($AUC_{0\text{-}24h}$, approximately 15-fold higher) than the exposure of filgotinib [see Section 6.2.1.1]. When filgotinib and GS-829845 were administered to CIA rat models in combination at a dose level equivalent to the exposure ratio seen in humans in a study to investigate the effect on ankle joint swelling [see Section 3.1.3], the effect of filgotinib treatment tended to be greater when combined with GS-829845 than when administered alone. The above result suggests that GS-829845 is considered to show a certain degree of effect against RA.

The applicant's explanation about the differences in mechanism of action between filgotinib and other JAK inhibitors, namely, tofacitinib, baricitinib, and upadacitinib, as well as their clinical impacts:
Tofacitinib inhibits mainly JAK1 and JAK3, baricitinib and upadacitinib inhibit mainly JAK1 and JAK2 while filgotinib mainly inhibits JAK1. Table 10 shows the percent inhibition of STAT phosphorylation over a 24-hour period calculated based on the blood concentrations of the JAK inhibitors including filgotinib at the maximum clinical dose and IC_{50} values for the JAK inhibitor in the *in vitro* assay using cytokine-stimulated whole blood. Percent STAT inhibition for JAK1/JAK2 and JAK1/TYK2 signaling was comparable among all the 4 JAK inhibitors. In contrast, filgotinib tended to inhibit non-JAK1-dependent signaling (JAK2/JAK2 and JAK2/TYK2) and primarily JAK3-dependent signaling (JAK1/JAK3) to a lesser degree than other JAK inhibitors studied.

Table10. Percent inhibition of STAT phosphorylation per 24-hour period at the maximum clinical dose of JAK inhibitors including filgotinib

Cell type	Stimulation	STAT phosphorylation studied	JAK involved	Inhibition (%)			
				FIL	TOFA	BARI	UPA
Monocytes	IL-6	STAT1	JAK1/JAK2	50	39	47	52
	IFNα	STAT5	JAK1/TYK2	55	55	62	72
	GM-CSF	STAT5	JAK2	7	9	22	29
	G-CSF	STAT3	JAK2/TYK2	14	21	36	29
	IFNγ	STAT1	JAK1/JAK2	10	17	29	29
NK cells	IL-15	STAT5	JAK1/JAK3	29	42	31	34
CD4-positive T cells	IL-2	STAT5	JAK1/JAK3	45	64	50	60
	IL-4	STAT6	JAK1/JAK3	28	47	36	47

FIL, filgotinib; TOFA, tofacitinib; BARI, baricitinib; UPA, upadacitinib
The effect of GS-829845 was also taken into account for the values of filgotinib.

PMDA concluded that the submitted data demonstrated the pharmacological action of filgotinib, and that it can be expected to be effective in treating RA. However, the results presented in Sections 3.1.1 and 3.1.2 do not necessarily demonstrate that filgotinib and GS-829845 are selective and specific inhibitors of JAK1. In addition, given that filgotinib also inhibits JAK2- or JAK3-mediated signaling to some degree (Table 10), effects on the immune system and hematopoietic system should be carefully considered when using filgotinib, as with other JAK inhibitors [see Section 7.R.3 for safety].

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted data from oral and intravenous studies in mice, rats, dogs, monkeys, and minipigs for evaluation of absorption, distribution, metabolism, and excretion. The plasma concentrations of filgotinib and its metabolites were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) with the following lower limits of quantitation: mice, 2 to 10 ng/mL (filgotinib) and 1 to 10 ng/mL (GS-829845); rats and dogs, 2 to 10 ng/mL (filgotinib) and 10 ng/mL (GS-829845); monkeys, 1 ng/mL (filgotinib) and 0.4 to 1 ng/mL (GS-829845); minipigs, 1 ng/mL (filgotinib) and 2 ng/mL (GS-829845). The radioactivity levels of

the samples were measured by liquid scintillation counter or quantitative whole-body autoradiography. Unless otherwise specified, dose levels are expressed as filgotinib free-base equivalent; pharmacokinetic parameters are presented as the mean or mean ± standard deviation.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.2, 4.2.2.2.3, 4.2.2.2.4, 4.2.2.2.9, 4.2.2.2.11, and 4.2.2.2.14)

Table 11 shows pharmacokinetic parameters following a single oral dose or intravenous administration of filgotinib to mice, rats, dogs, monkeys, or minipigs. The absolute bioavailability of oral filgotinib ranged as follows: 44.6% to 110% in mice; 40.6% in rats; 67.1% in dogs; 24.7% in monkeys; and 36.2% to 41.7% in minipigs.

Table 11. Pharmacokinetic parameters of filgotinib after a single dose of filgotinib

Species	Route of administration/ condition		Dose (mg/kg)	n	C_{max} (µg/mL)	AUC_{last} (µg·h/mL)	t_{max} (h)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
Mouse	Fasting	IV	1	3 males [a)]	—	0.32	—	2.87	6.03	—
		Oral	5	3 males [a)]	0.92	1.77	0.5	—	—	1.72
	Non-fasting	IV	1	3 males [a)]	—	0.44	—	1.86	10.4	8.43
		Oral	5	3 males [a)]	0.82	2.03	1.0	—	—	10.2
			30	3 males [a)]	6.07	7.27	0.25	—	—	—
Rat	Fasting	IV	1	3 males	—	0.72 ± 0.01	—	1.35 ± 0.03	1.76 ± 0.06	1.65 ± 0.03
		Oral	5	3 males	0.31 ± 0.10	1.43 ± 0.34	1.0 [0.5, 5.0]	—	—	3.94[b)]
Dog	Fasting	IV	1	2 males	—	3.84	—	0.24	1.64	7.47
		Oral	5	2 males	1.81	13.53	1.5	—	—	5.18
Monkey	Non-fasting	IV	1	3 males	—	1.33 ± 0.07	—	0.73 ± 0.04	3.13 ± 0.29	6.55 ± 0.60
		Oral	30	3 males	1.79 ± 0.16	9.94 ± 3.86	2.0 [2.0, 4.0]	—	—	—
Miniature pig	Fasting	IV	1	3 males	—	1.69 ± 0.26	—	0.63 ± 0.10	1.54 ± 0.27	3.87 ± 0.67
		Oral	5	3 males	0.36 ± 0.18	2.78 ± 1.05	4.0 [1.0, 6.0]	—	—	—
			30	3 males	2.16 ± 0.40	19.10 ± 3.65	4.0 [2.0, 4.0]	—	—	—

Mean or mean ± standard deviation; t_{max} is median or median [range] (data for mice, mean); —, not applicable or not calculated
a) number of animals per time point; b) n = 2

4.1.2 Repeated-dose studies (toxicokinetics) (CTD 4.2.3.2.9 and 4.2.3.2.11)

Table 12 shows the pharmacokinetic parameters of filgotinib and GS-829845 following repeated oral administration of filgotinib to rats and dogs. The filgotinib exposure increased roughly in a dose-proportional manner in both rats and dogs with no significant differences between the sexes. Data from repeated-dose administration of filgotinib showed no evidence of marked accumulation of GS-829845 in dogs, while a trend towards accumulation was seen in rats.

Table 12. Pharmacokinetic parameters of filgotinib and GS-829845 following repeated oral dose administration of filgotinib

Species	Analyte	n	Time point	Dose (mg/kg/day)	C_{max} (µg/mL)		AUC_{0-t} (µg·h/mL)		t_{max} (h)	
					Male	Female	Male	Female	Male	Female
Rat	Filgotinib	4/sex	Day 1	20	2.13 ± 0.57	3.10 ± 1.06	7.76 ± 0.40	8.46 ± 2.20	0.5 [0.5, 1.0]	0.8 [0.5, 1.0]
				45	5.84 ± 0.23	8.45 ± 0.62	26.86 ± 4.20	25.14 ± 5.53	1.0 [0.5, 1.0]	0.5 [0.5, 0.5]
				100	13.33 ± 1.39	14.30 ± 2.16	54.78 ± 8.25	56.74 ± 15.27	0.5 [0.5, 1.0]	0.5 [0.5, 0.5]
		4/sex	Day 178	20	4.75 ± 0.73	7.37 ± 2.02	16.10 ± 1.30	23.62 ± 9.43	0.8 [0.5, 1.0]	0.5 [0.5, 0.5]
				45	7.15 ± 1.57	10.91 ± 2.00	40.54 ± 6.44	43.56 ± 4.71	1.0 [1.0, 1.0]	0.5 [0.5, 0.5]
				100	18.03 ± 6.71	23.20 ± 7.34	83.94 ± 24.79	106.35 ± 22.08	0.8 [0.5, 1.0]	0.8 [0.5, 1.0]
	GS-829845	4/sex	Day 1	20	0.85 ± 0.74	1.42 ± 0.70	3.84 ± 1.28	8.16 ± 3.86	2.0 [1.0, 3.0]	1.0 [0.5, 3.0]
				45	1.39 ± 0.20	2.22 ± 0.57	11.68 ± 2.23	13.09 ± 1.67	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
				100	2.24 ± 0.24	2.93 ± 0.88	20.87 ± 3.10	23.56 ± 6.68	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
		4/sex	Day 178	20	1.15 ± 0.15	1.53 ± 0.27	6.88 ± 1.71	11.40 ± 4.60	1.0 [1.0, 1.0]	1.0 [1.0, 3.0]
				45	2.12 ± 0.51	2.61 ± 0.28	21.26 ± 4.07	23.54 ± 4.46	1.0 [1.0, 3.0]	1.0 [1.0, 3.0]
				100	5.08 ± 1.72	9.34 ± 5.05	50.00 ± 14.64	61.08 ± 9.01	1.0 [0.5, 8.0]	4.0 [1.0, 8.0]
Dog	Filgotinib	5/sex	Day 1	2.5	0.85 ± 0.13	0.92 ± 0.16	5.58 ± 1.30	6.19 ± 1.05	2 [1, 2]	1 [1, 1]
				5	1.81 ± 0.32	1.97 ± 0.43	10.85 ± 1.49	12.15 ± 2.96	1 [1, 2]	1 [1, 2]
				10	5.56 ± 0.38	4.75 ± 0.53	30.60 ± 3.78	30.65 ± 4.10	2 [1, 2]	1 [1, 1]
		5/sex	Day 267	2.5[a)]	1.05 ± 0.22	1.00 ± 0.25	5.13 ± 1.44	5.44 ± 1.40	2 [1, 2]	1 [1, 2]
				5	2.34 ± 0.44	2.77 ± 0.56	12.07 ± 1.41	13.74 ± 2.57	1 [1, 1]	1 [1, 2]
				10[b)]	4.49 ± 1.42	3.99 ± 1.49	22.53 ± 10.50	23.96 ± 12.94	1 [1, 2]	2 [1, 2]
	GS-829845	5/sex	Day 1	2.5	0.11 ± 0.01	0.09 ± 0.03	1.60 ± 0.21	1.26 ± 0.63	4 [4, 4]	4 [4, 8]
				5	0.21 ± 0.05	0.23 ± 0.04	3.16 ± 0.54	3.39 ± 0.99	4 [4, 4]	4 [4, 4]
				10	0.46 ± 0.15	0.55 ± 0.05	7.20 ± 2.12	8.18 ± 1.07	4 [4, 8]	4 [4, 4]
		5/sex	Day 267	2.5[a)]	0.16 ± 0.04	0.13 ± 0.04	2.53 ± 0.85	2.02 ± 0.65	4 [2, 4]	4 [2, 8]
				5	0.31 ± 0.08	0.35 ± 0.07	5.14 ± 1.40	5.68 ± 1.38	4 [2, 4]	4 [2, 8]
				10[b)]	0.51 ± 0.29	0.68 ± 0.25	7.15 ± 2.67	12.26 ± 6.73	3 [2, 4]	2 [2, 24]

Mean ± standard deviation; t_{max} is median [range]
a) Data of one of the males were measured on Day 274; b) 4 males

4.1.3 *In vitro* membrane permeability (CTD 4.2.2.2.1)

The membrane permeability of filgotinib was investigated using the human colon cancer-derived Caco-2 cell lines. The apparent permeability in the apical to the basal direction ($P_{app\ A\rightarrow B}$) ranged from 3.39×10^{-6} to 3.64×10^{-6} cm/s within the range of concentrations studied (1-100 µmol/L). The Papp $_{A\rightarrow B}$ for the low-permeability control compound atenolol (100 µmol/L) and the high-permeability control compound propranolol (10 µmol/L) was 0.15×10^{-6} and 20.1×10^{-6} cm/s, respectively.

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.2.13 and 4.2.2.3.6)

A single oral dose of ^{14}C-radiolabeled filgotinib[4)] (^{14}C-filgotinib or ^{14}C-carboxy-filgotinib) 60 mg/kg was administered to male albino rats and male pigmented rats to investigate tissue distribution[5)] of radioactivity up to 48 hours post-dose by quantitative whole-body autoradiography.

A single oral dose of radiolabeled compound was administered to male albino rats. For both compounds, radioactivity was distributed widely across the tissues immediately after administration. The radioactivity levels reached their maximum at 1-hour post-dose in the majority of the tissues. At 1 hour after administration of ^{14}C-filgotinib, the highest radioactivity, aside from the gastrointestinal tract, was detected in the bladder, followed by the liver, renal medulla, and renal cortex. At 48 hours post-dose, radioactivity decreased to below

[4)] Two compounds with varied radiolabeled sites were used: "^{14}C-filgotinib" and "^{14}C-carboxy-filgotinib." Radioactivity detected after administration of ^{14}C-filgotinib represents unchanged filgotinib, GS-829845, and their related metabolites, while that of ^{14}C-carboxy-filgotinib represents unchanged filgotinib, cyclopropanecarboxylic acid (CPCA), and their related metabolites.

[5)] Tissues studied include the adrenal gland, aorta, blood, brain, bone, epididymis, eye, renal cortex, renal medulla, lacrimal gland, liver, lung, preputial gland, skin, spleen, testis, inside and wall of the bladder, and gastrointestinal tract.

the detection limits in all tissues except for the gastrointestinal tract, skin, and bladder wall. Following administration of ^{14}C-carboxy-filgotinib, radioactivity was high in the Harderian gland, brown adipose, lacrimal gland, and epididymis, in addition to the gastrointestinal tract.

Following a single oral dose of each radiolabeled compound to male pigmented rats, high radioactivity concentrations were detected in the uveal tract of the eye, demonstrating that filgotinib has an affinity for melanin-containing tissues. In other tissues, radioactivity was distributed in a similar manner as in albino rats.

4.2.2 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3.1, 4.2.2.3.2, 4.2.2.3.4, 4.2.2.3.5, and 4.2.2.3.7)

Plasma protein binding of filgotinib at the tested concentrations (2-10 µmol/L) measured by equilibrium dialysis was 29% to 65% in mice, 51% to 52% in rats, 70% in rabbits, 36% in dogs, and 32% in monkeys. In humans, plasma protein binding was 36% to 55%.

Plasma protein binding of GS-829845 at the tested concentrations (2-56 µmol/L) measured by equilibrium dialysis was 26% to 55% in mice, 39% to 53% in rats, 55% in rabbits, and 25% to 29% in dogs. In humans, plasma protein binding was 32% to 34%.

The blood-to-plasma concentration ratio in mice, rats, dogs, minipigs, and monkeys ranged from 0.81 to 1.29 for filgotinib and 0.89 to 1.52 for GS-829845 (at 0.5 or 2 µmol/L for both filgotinib and GS-829845). In humans, the blood-to-plasma concentration ratio was 1.02 for filgotinib and 1.39 for GS-829845.

4.2.3 Placental transfer

Studies in rats and rabbits showed that filgotinib and GS-829845 are teratogenic. Since filgotinib treatment is contraindicated in women who are or may be pregnant [see Section 5.5 and 5.R.3.2], placental transfer of filgotinib is not evaluated.

4.3 Metabolism

4.3.1 *In vitro* study (CTD 4.2.2.4.2, 4.2.2.4.3, 4.2.2.4.5, and 4.2.2.4.6)

Filgotinib (70.6 µmol/L) was incubated with human liver microsomes in the presence or absence of nicotinamide adenine dinucleotide phosphate (NADPH) for 1 hour. Filgotinib was metabolized to form GS-829845, and an addition of a carboxylesterase (CES) inhibitor (bis-*p*-nitrophenyl phosphate, 20 or 100 µmol/L) inhibited formation of GS-829845.

Filgotinib (6 or 60 µmol/L) was incubated with recombinant human CES1b, CES1c, or CES2, and the metabolic activity of filgotinib into GS-829845 was measured. The activity with CES2 was approximately 5-fold higher than those with CES1b or CES1c. In addition, the metabolic activity was inhibited by adding loperamide, a selective CES2 inhibitor, suggesting that CES2 is predominantly involved in the metabolism of filgotinib.

Cryopreserved hepatocytes from mice, rats, dogs, monkeys, and humans were incubated with ^{14}C-labeled filgotinib (100 μmol/L) for 24 hours. Unchanged ^{14}C-labeled filgotinib decreased by 14.6% (mouse), 14.4% (rat), 7.1% (dog), 19.6% (monkey), and 7.5% to 18.2% (human). Metabolite GS-829845 was isolated and identified in hepatocytes from all animal species including humans. Furthermore, a metabolite formed by dehydrogenation of the 1,1-dioxo-thiomorpholine ring (M3) was identified in rat hepatocytes. In monkey hepatocytes, in addition to M3, a metabolite formed by oxidation of the 1,1-dioxo-thiomorpholine ring (M1) was also identified. No human specific metabolites were found.

4.3.2 *In vivo* studies (CTD 4.2.2.4.1, 4.2.2.4.4, 4.2.2.5.1, 4.2.2.5.2, 4.2.2.5.3, and 5.3.3.1.3)

Table 13 shows metabolites formed in samples when a single oral dose or repeated oral doses of filgotinib or ^{14}C-labeled filgotinib were administered to transgenic rasH2 mice, rats, dogs, and monkeys. The results of a foreign mass balance study [see Section 6.2.1.2] showed no human specific metabolites.

Table 13. Metabolite profiles for different animal species

Species	Regimen	n	Plasma	Bile	Feces	Urine	CTD
Mouse	50 mg/kg Single oral dose	3 males/time point or 4 males	Up to 12 hours post-dose Unchanged parent compound, GS-829845, GS-829845-N-glucuronide, M8, M9, and CPCA-related metabolites		Up to 48 hours post-dose Unchanged parent compound, GS-829845, M3, GS-829845-N-glucuronide, M7, M8, M9, and CPCA-related metabolites	Up to 24 hours post-dose Unchanged parent compound, GS-829845, M1, M4, GS-829845-N-glucuronide, M8, M9, and CPCA-related metabolites	4.2.2.4.1 4.2.2.5.1
Rat	45 mg/kg/day Repeated oral doses	3 males	Up to 24 hours post-dose Unchanged parent compound, GS-829845, and M3				4.2.2.4.4
	10 mg/kg Single oral dose	3 males[a)]	Up to 24 hours post-dose Unchanged parent compound, and GS-829845	Up to 24 hours post-dose Unchanged parent compound, and GS-829845	Up to 24 hours post-dose Unchanged parent compound, and GS-829845	Up to 24 hours post-dose Unchanged parent compound, and GS-829845	4.2.2.5.2
Dog	15 mg/kg Single oral dose	3 males	Up to 48 hours post-dose Unchanged parent compound, GS-829845, GS-829845-N-glucuronide, M1, M1-O-glucuronide, M3, CPCA-related metabolites, and metabolites with unidentified structure		Up to 168 hours post-dose Unchanged parent compound, GS-829845, GS-829845-N-glucuronide, M1, M1-O-glucuronide, M3, and metabolites with unidentified structure	Up to 168 hours post-dose Unchanged parent compound, GS-829845, GS-829845-N-glucuronide, M1, M1-O-glucuronide, M3, CPCA-related metabolites, and metabolites with unidentified structure	4.2.2.5.3
	5 mg/kg/day Repeated oral doses	3 males	Up to 24 hours post-dose Unchanged parent compound, GS-829845, and M3				4.2.2.4.4
Monkey	30 mg/kg Single oral dose	3 males	Up to 24 hours post-dose Unchanged parent compound, GS-829845, and M3				4.2.2.4.4

CPCA-related metabolites: CPCA, CPCA-glycine, CPCA-carnitine, CPCA-taurine
a) Bile duct cannulated rats

Figure 1 shows metabolic pathways of filgotinib estimated based on the findings from the above studies on metabolism.

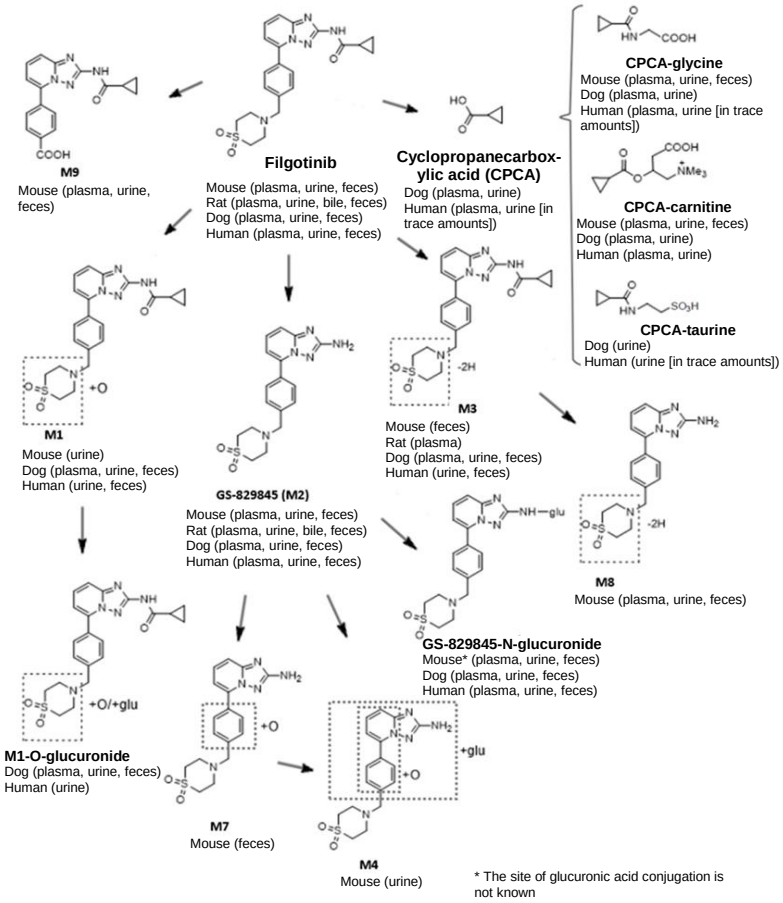


Figure 1. Estimated metabolic pathways of filgotinib in mice, rats, dogs, and humans

4.4 Excretion

4.4.1 Urinary and fecal excretion and biliary excretion (CTD 4.2.2.4.1, 4.2.2.5.1, 4.2.2.5.2, and 4.2.2.5.3)

A single oral dose of ^{14}C-labeled filgotinib 50 mg/kg was administered to transgenic rasH2 mice (4 males). The mean total recovery[6)] of radioactivity up to 72 hours post-dose was 96.1%, with urinary and fecal excretion being 37.7% and 54.0% of the total radioactivity, respectively. Up to 24 hours post-dose, 37.4% of the radioactivity administered was excreted in urine, with major constituents being GS-829845 (9.85%) and unchanged ^{14}C-labeled filgotinib (9.34%). The other metabolites detected were M1, M4, GS-829845-N-glucuronide, M8, and M9. Up to 48 hours post-dose, 53.9% of the radioactivity administered was excreted in feces, with major constituents being unchanged ^{14}C-labeled filgotinib (27.1%) and GS-829845 (13.8%). The other metabolites detected were M3, GS-829845-N-glucuronide, M7, M8, and M9.

A single oral dose of ^{14}C-labeled filgotinib 10 mg/kg was administered to bile duct cannulated rats (3 males). The mean total recovery of radioactivity up to 24 hours post-dose was 88.9%. While biliary and urinary excretion was 14.9% and 16.0%, respectively, 46.9% of the radioactivity administered was excreted in feces not via the bile. Up to 24 hours post-dose, unchanged ^{14}C-labeled filgotinib (1.8%) and GS-829845 (0.41%)

6) In addition to radioactivity in urine and feces, radioactivity recovered from carcasses of the animals studied and cage rinses was also included in the calculation of the mean total recovery.

were excreted in bile. From 6 to 24 hours post-dose, unchanged ^{14}C-labeled filgotinib (7.7%) and GS-829845 (2.4%) were excreted in urine, and unchanged ^{14}C-labeled filgotinib (5.9%) and GS-829845 (0.24%) were excreted in feces.

A single oral dose of ^{14}C-labeled filgotinib 15 mg/kg was administered to dogs (2 males). The mean total recovery of radioactivity up to 168 hours post-dose was 90.1%, with urinary and fecal excretion being 25.2% and 58.6%, respectively. The major forms of radioactivity detected in urine were unchanged ^{14}C-labeled filgotinib (16.6%) and GS-829845 (4.49%). The other metabolites detected were GS-829845-N-glucuronide, M1, M1-O-glucuronide, M3, as well as metabolites with an unidentified structure. In feces, unchanged ^{14}C-labeled filgotinib (32.2%) and GS-829845 (2.72%) were the major forms of radioactivity. The other metabolites detected were GS-829845-N-glucuronide, M1, M1-O-glucuronide, M3, as well as metabolites with an unidentified structure.

4.4.2 Excretion into breast milk (CTD 4.2.3.5.3.1)

In the study of effects on pre- and postnatal development, including maternal function in rats [see Section 5.5], filgotinib or GS-829845 was administered orally once daily to dams. The $AUC_{0\text{-}24h}$ of filgotinib and GS-829845 in dams and fetuses at 10 days postpartum/after birth (Table 14) suggested that filgotinib and GS-829845 can be excreted into breast milk [see Section 5.R.3.2 regarding the need for caution statement].

Table 14. $AUC_{0\text{-}24h}$ (ng·h/mL) at 10 days postpartum/after birth following oral administration of filgotinib or GS-829845 to dams

	Filgotinib 15 mg/kg		GS-829845 30 mg/kg	
	Dam	Pup	Dam	Pup
Filgotinib	8,320	469		
GS-829845	4,940	412	48,000	1,860

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition and induction (CTD 4.2.2.6.11, 4.2.2.6.12, 4.2.2.6.14, and 4.2.2.6.17)

Using human liver microsomes, the inhibitory effects of filgotinib and GS-829845 on human cytochrome P450 (CYP) isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) were investigated.[7)] For these CYP isoforms, the IC_{50} values were >70.6 μmol/L (filgotinib) and >224 μmol/L (GS-829845), respectively. No time-dependent inhibition was observed.

The inhibitory effects of filgotinib and GS-829845 on recombinant human uridine diphosphate glucuronosyltransferase (UGT) isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) were investigated.[8)] The IC_{50} values were >60 μmol/L (filgotinib) and >80 μmol/L (GS-829845) for the UGT isoforms studied.

[7)] In this study, prior to adding a substrate, filgotinib or GS-829845 was pre-incubated with the test systems to assess whether they exhibit time-dependent inhibition. The following compounds were used as substrates for the CYP isoforms: phenacetin for CYP1A2; coumarin for CYP2A6; bupropion for CYP2B6; paclitaxel for CYP2C8; tolbutamide for CYP2C9; *S*-mephenytoin for CYP2C19; dextromethorphan for CYP2D6; chlorzoxazone for CYP2E1; midazolam, testosterone, and nifedipine for CYP3A4/5.

[8)] The following compounds were used as substrates for the UGT isoforms: β-estradiol for UGT1A1; trifluoperazine for UGT1A4; deferiprone for UGT1A6; propofol for UGT1A9; zidovudine for UGT2B7.

Using human hepatocytes, the induction of filgotinib (3-60 μmol/L) and GS-829845 (10-350 μmol/L) on the mRNA expression of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) were investigated. While abnormal changes in CYP2B6 mRNA expression attributable to suppressed glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in response to cell stress were observed in one of 3 donors of human hepatocytes, there was no increase in mRNA expression for any of the CYP isoforms.

The applicant's explanation:
In addition to the above results, findings including C_{max} data of filgotinib and GS-829845 following multiple doses of filgotinib 200 mg orally once daily to patients with RA (filgotinib, 1.01 μg/mL [2.38 μmol/L]; GS-829845, 3.49 μg/mL [9.76 μmol/L]; [see Section 6.3]) and investigation using the mechanistic static model indicate that filgotinib and GS-829845 are unlikely to inhibit or induce the enzymes described above at clinically relevant doses.

4.5.2 Substrates for drug transporters (CTD 4.2.2.6.2 and 4.2.2.6.3)

Filgotinib and GS-829845 were evaluated using Madin-Darby canine kidney (MDCK) II cells expressing human P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP), or Chinese hamster ovary (CHO) cells expressing organic anion transporting polypeptide (OATP)1B1 or OATP1B3.[9)] The results suggest that filgotinib and GS-829845 may be substrates for P-gp.

4.5.3 Inhibition of drug transporters (CTD 4.2.2.6.5, 4.2.2.6.6, 4.2.2.6.8, 4.2.2.6.9, 4.2.2.6.10, 4.2.2.6.12, 4.2.2.6.13, and 4.2.2.6.16)

The inhibitory effects of filgotinib and GS-829845 on drug transporters[10)] were evaluated using CHO cells expressing human OATP1B1, OATP1B3, organic anion transporter (OAT)1, organic cation transporter (OCT)1, or OCT2, MDCKII cells expressing human P-gp, BCRP, multidrug and toxin extrusion (MATE)1, MATE2-K, OAT2, OCT2, or OCT3, membrane vesicles expressing human bile salt export pump (BSEP), and human embryonic kidney cells 293 (HEK293 cells) expressing human OAT3 or OCT1 (Table 15).

The applicant's explanation:
In addition to the above, results including C_{max} of filgotinib and GS-829845 following administration of filgotinib 200 mg orally once daily to patients with RA (filgotinib, 1.01 μg/mL [2.38 μmol/L]; GS-829845, 3.49 μg/mL [9.76 μmol/L]; [see Section 6.3]) and investigation using the mechanistic static model indicate that filgotinib may inhibit OCT2, MATE1, and MATE2-K while GS-829845 may inhibit OCT2 and MATE2-K at clinically relevant doses.

[9)] The following compounds were used as inhibitors for the transporters: ciclosporin A for P-gp; Ko134 for BCRP; rifampicin for OATP1B1 and OATP1B3.
[10)] The following compounds were used as substrates for the transporters: calcein AM for P-gp; pheophorbide A and prazosin for BCRP; fluo-3 for OATP1B1; fluo-3 for OATP1B3; p-aminohippuric acid for OAT1; creatinine for OAT2; estrone-3-sulfate for OAT3; tetraethylammonium for OCT1; metformin, creatinine, and tetraethylammonium for OCT2; creatinine for OCT3; creatinine for MATE1; metformin for MATE2-K; taurocholate for BSEP.

Table 15. Inhibition of drug transporters by filgotinib and GS-829845

Transporter	Analyte	Concentration studied (μmol/L)	IC_{50} (μmol/L) (max. inhibition)	Transporter	Analyte	Concentration studied (μmol/L)	IC_{50} (μmol/L) (max. inhibition)
P-gp	Filgotinib	0.82-200	>200 (3.0%)	OCT1	Filgotinib	0.48-350	151.6 (72.9%)
	GS-829845	0.17-40	>40 (—)		GS-829845	0.69-500	140 (83.1%)
BCRP	Filgotinib	0.17-200	>200 (20.9%)	OCT2	Filgotinib	0.14-350	8.7 (98.8%)
	GS-829845	0.17-50	>50 (—)		GS-829845	0.14-500	14.9 (92.0%)
OATP1B1	Filgotinib	0.48-350	110 (84.5%)	OCT3	Filgotinib	0.95-300	188 (69.3%)
	GS-829845	0.69-500	90 (91.9%)		GS-829845	0.95-300	>300 (26.0%)
OATP1B3	Filgotinib	0.48-350	168 (77.5%)	MATE1	Filgotinib	0.95-300	8.63 (90.7%)
	GS-829845	0.69-500	158 (81.3%)		GS-829845	0.95-300	>300 (48.7%)
OAT1	Filgotinib	0.13-100	>100 (—)	MATE2-K	Filgotinib	0.95-300	5.21 (97.1%)
	GS-829845	0.41-300	>300 (—)		GS-829845	0.95-300	10.9 (85.0%)
OAT2	Filgotinib	0.95-300	>300 (43.7%)	BSEP	Filgotinib	0.23-170	>170 (—)
	GS-829845	0.95-300	>300 (11.4%)		GS-829845	0.69-500	>500 (—)
OAT3	Filgotinib	0.13-100	>100 (—)				
	GS-829845	0.41-300	>300 (21.0%)				

—, no inhibition

4.R Outline of the review conducted by PMDA

The study results suggested that filgotinib has an affinity for melanin-containing tissues. The applicant's explanation about the effect of filgotinib on melanin-containing tissues:

In view of the following study outcomes, filgotinib and GS-829845 are unlikely to raise safety concerns regarding accumulation in melanin-containing-tissues: the results of repeated-dose toxicity studies in rats and dogs provided no significant ophthalmological findings or histopathological findings of the eye [see Section 5.2]; in the phototoxicity study in pigmented rats, the results of the ophthalmological tests, local skin reaction, and histopathological study in the eye and the eyelid did not raise any concern that filgotinib and/or GS-829845 could be phototoxic [see Section 5.8.2].

PMDA accepted the above explanation and concluded that the *in vivo* behavior of filgotinib can be understood to certain extent, based on the data submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The results of the following toxicity studies were submitted: single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, juvenile animal toxicity, local tolerance, and other toxicity studies (skin sensitization, phototoxicity, immunotoxicity, mechanistic study on toxicity, toxicity of metabolites, and impurities).

5.1 Single-dose toxicity

Acute toxicity of filgotinib was evaluated in a single oral dose toxicity study in dogs (Table 16). Acute symptoms noted were vomiting and salivation. In the 14-day repeated-dose toxicity study in rats (CTD 4.2.3.2.1), no deaths occurred at ≤180 mg/kg, and the approximate lethal dose was determined to be >180 mg/kg. No acute symptoms were noted. In the 4-week repeated-dose toxicity study in mice (CTD 4.2.3.2.13), deaths associated with exacerbated clinical signs (e.g., hunchback position, piloerection, inanimation, ataxic gait, decreased grasp reflex, incomplete eyelid opening, gasping, abdominal breathing, and cold sensation) occurred at 1,500 mg/kg, and the approximate lethal dose was determined to be 1,500 mg/kg.

Table 16. Summary of the single-dose toxicity study

Test system	Route of administration (Agent)	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Male/female dog (beagle)	Oral (Filgotinib)	10, 30, and 100	100 mg/kg (Vehicles 1 and 3), vomiting 100 mg/kg (Vehicle 2), salivation	>100	4.2.3.1.1

Vehicle 1, 40% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPBCD) aqueous solution; Vehicle 2, polyethylene glycol (PEG)400 and 2% citric acid monohydrate; Vehicle 3, a mixture of PEG400 and 30% (w/v) HPBCD aqueous solution (20/80, v/v)

5.2 Repeated-dose toxicity

Rat repeated-dose toxicity studies of filgotinib and its major human metabolite GS-829845 via the oral route of administration were conducted (Table 17). The no-observed adverse effect level (NOAEL) was 20 mg/kg/day for males and 45 mg/kg/day for females in the rat 6-month repeated-dose toxicity study. The filgotinib $AUC_{0\text{-}24h}$ values at Week 26 following administration at the NOAEL were 16.1 μg·h/mL for males and 43.6 μg·h/mL for females, corresponding to approximately 3.6-fold (males) and 9.8-fold (females), respectively, to the clinical exposure[11)] (AUC_{tau}, 4.45 μg·h/mL).

Major systemic toxicity or abnormal findings of filgotinib were low blood leukocyte/lymphocyte parameters, decreased cellularity/depletion of lymphoid tissue, reduced spermatogenesis in the testis (e.g., depletion/degeneration/vacuolation of germ cells, and decreased sperm counts), incomplete enamel formation in the incisor, low erythrocyte parameters, pigmentation in the liver, spleen, and other tissues, and high blood luteinizing hormone (LH) levels. The observed reduction in immune cell counts in blood and lymphoid tissues is an effect associated with the inhibition of JAKs by filgotinib and was reversible; therefore, these events were not considered to be toxicity findings. Striation in the incisor tooth enamel was observed in the 6-month repeated-dose toxicity study in rats; however, it was not considered to be toxicity findings because of the absence of anomalies in the enamel matrix. No new toxicities were identified for GS-829845 other than those observed for filgotinib.

Table 17. Summary of repeated-dose toxicity studies in rats

Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
Male/female rats (SD)	Oral gavage (filgotinib)	4 weeks (once daily) + 2-week recovery period	0, 5, 15, 45	≥5 mg/kg: decrease in bone marrow cellularity, decrease in aggregation of lymphocytes in the spleen lymphoid tissue (males and females); low blood leukocyte/lymphocyte/neutrophil/monocyte/basophil count, low large unstained cell count in blood (females) ≥15 mg/kg: salivation[1)] (males and females); low spleen weight (females) 45 mg/kg: low blood neutrophil/basophil count, low spleen weight (males) The findings were reversible	Filgotinib 45	4.2.3.2.3
Male/female rats (SD)	Oral gavage (filgotinib, GS-829845)	3 months (once daily) + 8-week recovery period	Filgotinib 0, 20, 60, 180 GS-829845 60, 180	**Filgotinib** ≥20 mg/kg: low blood leukocyte count, low percentage of blood cytotoxic T cells, low spleen weight (males and females); salivation,[1)] low blood lymphocyte/eosinophil count, adrenal fasciculata vacuolation,[2)] centrilobular hepatocyte hypertrophy in the liver[2)] (males); splenic/mesenteric lymphoid tissue atrophy (females)	Filgotinib 20 (male) 60 (female) GS-829845 180	4.2.3.2.7

[11)] The exposure level of filgotinib following repeated oral dose administration of filgotinib at the recommended clinical dose (200 mg/day) to Japanese patients with RA [see Section 6.3]

Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
				≥60 mg/kg: low blood lymphocyte count, low percentage of blood helper T cells, high MCV, reduced thymus size, increase in splenic hemosiderin deposition,[2)] decrease in inflammatory foci in the liver (males and females); low testicular weight, low epididymal weight, low liver weight, softening/reduced size of the testis and epididymis, reduced size of the spleen, decrease in sperm count/motility/healthy sperm count in the efferent duct, low sperm volume in the testis and epididymis, atrophy of seminiferous tubules/loss of germ cells/giant sperm cells/Leydig cell hyperplasia/germ cell degeneration in the testis, decrease in epididymal sperm count, epididymal cell debris, lymphoid tissue atrophy in the spleen, lymphoid tissue atrophy in submandibular lymph nodes, increase in adipocytes in the bone marrow, hypertrophic cells in the anterior pituitary gland,[2)] pigmentation in hepatic Kupffer cells (males); salivation,[1)] low blood lymphocyte count, low erythrocyte count,[2)] low blood urea/creatinine levels,[2)] apoptosis in the exocrine pancreas,[2)] lymphoid tissue atrophy in the thymus (females) 180 mg/kg: low percentage of blood T cells, low percentage of blood NK cells, high erythrocyte distribution width, low hemoglobin, low hematocrit, high blood AST/ALP levels, high blood A/G ratio, high blood inorganic phosphate levels,[2)] low total protein/globulin/calcium levels in blood,[2)] high urine volume,[2)] low urine specific gravity,[2)] low thymus/kidney weight, reduced size of splenic red pulp, lymphoid tissue atrophy in Peyer's patches, foamy pulmonary macrophages, pigmentation in renal tubules[2)] (males and females); low body weight, low erythrocyte count, high blood ALT,[2)] low prostate/seminal vesicle weight, increase in decapitated sperm,[3)] lymphoid tissue atrophy in thymic/mesenteric lymph nodes, decrease in myeloid cells, apoptosis in the exocrine pancreas, decrease in zymogen granules in the pancreas,[2)] chronic progressive nephrosis, high blood LH/FSH levels, low blood inhibin B (males); low blood eosinophil count, high reticulocyte count, low liver weight, reduced spleen size, lymphoid tissue atrophy in mandibular lymph nodes, hypertrophic cells in the anterior pituitary gland, [2)] adrenal fasciculata vacuolation,[2)] pigmentation in hepatic Kupffer cells (females) 60 mg/kg: stagnant sperm/vacuolation in the testicular seminiferous tubules, circumscribed germ cell loss (males); increase in adipocytes in the bone marrow (females) **GS-829845** ≥60 mg/kg: low blood leukocyte/lymphocyte count, low percentage of blood cytotoxic T cells, low percentage of blood helper T cells, low spleen weight, decrease in inflammatory foci in the liver (males and females); low blood eosinophil count, low percentage of blood cytotoxic T cells, reduced size of the spleen/thymus, increase in splenic hemosiderin deposition,[2)] lymphoid tissue atrophy in mesenteric lymph nodes, increase in adipocytes in the bone marrow (males); lymphoid tissue atrophy in the spleen, high blood AST[2)] (females) 180 mg/kg: lymphoid tissue atrophy in thymus/submandibular lymph nodes (males and females); salivation,[1)] low body weight,[2)] high blood AST/ALP levels, high blood A/G ratio,[2)] low thymus weight, reduced size of splenic red pulp, lymphoid		

Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
				tissue atrophy in the spleen/Peyer's patches, adrenal fasciculata vacuolation,[2)] apoptosis in the exocrine pancreas,[2)] foamy pulmonary macrophages, pigmentation in renal tubules[2)] (males); low blood eosinophil count, low blood urea/creatinine levels,[2)] reduced size of the spleen/thymus, lymphoid tissue atrophy in mesenteric lymph nodes, increase in adipocytes in the bone marrow (females) 60 mg/kg: reduced size of splenic white/red pulp (males) 180 mg/kg: reduced size of splenic white/red pulp (females) The findings were reversible		
Male/female rats (SD)	Oral gavage (filgotinib, GS-829845)	6 months (once daily)	Filgotinib 0, 20, 45, 100 GS-829845 75, 150	**Filgotinib** ≥20 mg/kg: low blood leukocyte/lymphocyte/eosinophil/basophil/T cell/helper T cell/cytotoxic T cell/B cell/NK cell count, low spleen weight (males and females); salivation,[1)] decrease in infiltration of inflammatory cells in the liver (females); ≥45 mg/kg: striation in incisor tooth enamel (males and females); salivation,[1)] high blood LH, low percentage of motile sperm, low percentage of normal-shaped sperm, low mean epididymal sperm count/weight, low epididymal weigh, low seminal vesicle weight, low pituitary weight, testicular atrophy/degeneration, interstitial edema, decrease in epididymal sperm count, increase in exfoliated germ cells in the epididymis, loss of germinal centers in mandibular lymph nodes, increase in adipocytes in the bone marrow (males); low MCH, low blood glucose,[2)] high inorganic phosphate,[2)] high calcium oxalate in urine, lymphoid tissue atrophy in the thymus, increase in vacuolation in renal tubules (females) 100 mg/kg: whitening of incisors, low erythrocyte count, low hemoglobin, low hematocrit, low MCV, high platelet count, high blood ALP,[2)] low thymus weight, reduced size of the thymus, faded white color of the incisor, loss of germinal centers in mesenteric lymph nodes, lymphoid tissue atrophy in mesenteric lymph nodes, decrease in periarterial lymphatic sheath in the spleen, foamy macrophages in pulmonary lobules, pigmentation in the liver, loss of germinal centers in GALT, degenerative loss/disruption of incisor ameloblasts, incomplete enamel formation in the incisor (males and females); low body weight, low food consumption, low MCH, low blood testosterone, low blood inhibin B, high blood FSH, high blood inorganic phosphate,[2)] high calcium oxalate in urine, low number of testicular sperm heads, low daily sperm production, low prostate weight, low weight/reduced size of the testis, reduced size of the epididymis, reduced size of the spleen, pituitary enlargement, increase in vacuolated pituitary cells, lymphoid tissue atrophy in the thymus, increase in splenic pigmentation, increase in vacuolation in the adrenal gland, decrease in infiltration of inflammatory cells in the prostate/liver, GALT lymphoid tissue atrophy, increase in pituitary LH/FSH-positive cells (males); pigmentation in renal tubules, increase in adipocytes in the bone marrow (females) **GS-829845** ≥75 mg/kg: salivation,[1)] piloerection,[2)] low blood leukocyte/lymphocyte/T cell/helper T cell/cytotoxic T cell/B cell/NK cell count, low spleen weight,	Filgotinib 20 (male) 45 (female) GS-829845 150	4.2.3.2.9

Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
				decrease in infiltration of inflammatory cells in the liver (males and females); hunchback position,[2] low pituitary weight, loss of germinal centers in mandibular lymph nodes, increase in adipocytes in the bone marrow, decrease in infiltration of inflammatory cells in the prostate (males); low blood eosinophil count (females) 150 mg/kg: decrease in periarterial lymphatic sheath in the spleen (males and females); low body weight, low food consumption,[2] low blood basophil count (males); hunchback position,[2] high blood ALP,[2] high calcium oxalate in urine, loss of germinal centers in mesenteric lymph nodes, loss of germinal centers in GALT, increase in adipocytes in the bone marrow (females)		

Vehicle, 0.5% methylcellulose (MC) aqueous solution
1) The event can be attributed to the oral gavage procedure, as well as to the unpalatable/texture of the liquid agent, and was assessed to be of low toxicological significance.
2) The findings are assessed to be of low toxicological significance for reasons including the following: changes are within the range of historical control data at the laboratory or transient in nature, absence of related abnormal/toxicological findings, or degree of severity.
3) The testing was performed only in 180 mg/kg males.

Repeated-dose oral toxicity studies of filgotinib and GS-829845 were conducted using dogs (Table 18). The NOAEL in the dog 9-month repeated-dose toxicity study was 5 mg/kg/day for males and 10/7.5/10 mg/kg/day for females. After repeated-dose administration at these dose levels, filgotinib $AUC_{0\text{-}24h}$ values at Week 39 were 12.1 µg·h/mL for males and 24.0 µg·h/mL for females, corresponding to approximately 2.7-fold (males) and 5.4-fold (females), respectively, to the clinical exposure[11] (AUC_{tau}, 4.45 µg·h/mL).

Major systemic toxicity or abnormal findings of filgotinib were low blood leukocyte/lymphocyte parameters, decreased cellularity/depletion of lymphoid tissue, canine papillomavirus-induced cutaneous nodules (warts) or demodex infection-related lesions due to immunosuppression, abnormal spermatogenesis in the testis (e.g., depletion/degeneration/vacuolation of germ cells, and decreased sperm counts), low erythrocyte parameters, brown pigmentation in the spleen and liver, increased extramedullary hematopoiesis in the spleen, oral mucosa ulcers, and damage to gastric/small intestinal mucosa. The reduction in immune cell counts in blood and lymphoid tissues, together with abnormal findings related to the immunosuppressive effect are effects associated with the inhibition of JAKs by filgotinib and were reversible; therefore, these findings were not considered to be toxicity findings. The abnormal testicular findings did not show adequate reversibility even after the 8-week recovery period. Abnormal testicular findings were not classified as toxic if epididymal anomalies were absent in terms of sperm count and spermatogenesis. No new toxicities were identified for GS-829845 other than those observed for filgotinib.

Table 18. Summary of repeated-dose toxicity studies in dogs

Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
Male/ female dogs (beagle)	Oral gavage (filgotinib)	4 weeks (once daily) + 2-week recovery period	0 , 5, 15, 30	<u>Dead animals[1)] (1 male, 1 female)</u> 30 mg/kg: salivation,[2)] hypolocomotion, vomiting, decrease in food consumption, low body weight, low reticulocyte/leukocyte/lymphocyte/platelet count, high neutrophil count, increase in blood fibrinogen, low inorganic phosphate, high blood AST, high globulin, high cholesterol, hemorrhage/inflammation in submandibular lymph nodes, gums, and large intestine, decrease in erythroblast cellularity/granulocyte count/lymphoid tissue in the bone marrow, atrophy of osteoblasts, degeneration/cell debris in the rectal gland/jejunum/ileal crypts, acute inflammation/glandular cell single cell necrosis/ductal dilation of the salivary gland, seminiferous epithelium degeneration of the testis, epididymal multinucleated cells, decrease in sperm cellularity, single cell necrosis of the stomach <u>Surviving animals</u> ≥5 mg/kg: increase in adipocytes in the bone marrow, loss of glycogen granules from the liver (males and females); decrease in granular myeloid cells in bone marrow (males) ≥15 mg/kg: low hematocrit, low eosinophil/basophil count, high blood APTT, reduced size of splenic lymphoid follicles, reduced size of periarterial lymphatic sheath, decrease in lymphocyte cellularity, reduced size of thymic cortex, decrease in thymic lymphocyte cellularity, thymic lymphocyte necrosis/phagocytic macrophage, loss of cortico-medullary junction of the thymus, reduced size of lymphoid follicles in submandibular/mesenteric lymph nodes, decrease in lymphocyte cellularity, reduced size of lymphoid follicles/decrease in lymphocyte cellularity in Peyer's patches, reduced size of the duodenal/small intestinal/large intestinal GALT, decrease in lymphocyte cellularity (males and females); low erythrocyte count, low hemoglobin, low reticulocyte count, low blood leukocyte count, low blood lymphocyte count, low blood neutrophil count, low blood inorganic phosphate, low thymus weight, low testicular weight, reduced size of GALT in the stomach, decrease in gastric lymphocyte cellularity, degeneration of seminiferous tubule epithelium in the testis, multinucleated sperm cells in the testis, decrease in epididymal sperm cellularity, degeneration of germ cells (males) 30 mg/kg: salivation,[2)] low spleen weight (males and females); low erythrocyte count, low hemoglobin, low reticulocyte count, high blood leukocyte count, high blood lymphocyte count, high blood neutrophil count, low thymus weight, reduced size of GALT in the stomach, decrease in gastric lymphocyte cellularity (females) 15 mg/kg: decrease in granular myeloid cells in bone marrow (females) Reversibility The findings were reversible except for testicular toxicity-related findings	5	4.2.3.2.5
Male/ female dogs (beagle)	Oral gavage (Filgotinib, GS-829845)	3 months (once daily + 8-week recovery period	Filgotinib 0, 2.5, 6, 15 GS-829845 20, 50	**Filgotinib** ≥2.5 mg/kg: increased extramedullary hematopoiesis in the spleen (males and females); brown pigmentation in hepatic Kupffer cells (males) ≥6 mg/kg: low blood inorganic phosphate, testicular germ cell degeneration,[3)] low normal motile sperm count, increase in multinucleated giant spermatids in the testis, increase in epididymal cell debris, lymphocytic infiltration of the prostate, decrease in lymphocytes in mesenteric lymph node sinuses (males); low blood eosinophil count, high blood APTT/AST levels[4)] (females) 15 mg/kg: low erythrocyte count, low erythrocyte distribution width, low hemoglobin, low hematocrit, low percentage of blood T cells/helper T cells/cytotoxic T cells (males and females); salivation,[2)] vomiting, low blood leukocyte/lymphocyte/eosinophil count, high blood APTT/AST levels,[4)] low total sperm count in semen, low weight/reduced size	Filgotinib 6 (male) 15 (female) GS-829845 50	4.2.3.2.8

Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
				of the testis/epididymis, testicular germ cell depletion, decrease in epididymal sperm count, congestion of the spleen, lymphoid tissue atrophy in mesenteric lymph nodes (males); high blood total bilirubin,[4)] low blood inorganic phosphate,[4)] decrease in zymogen granules in the pancreas (females) **GS-829845** ≥20 mg/kg: low blood eosinophil count (males and females); salivation,[2)] high heart rate,[4)] lymphocytic infiltration of the prostate (males); increased extramedullary hematopoiesis in the spleen, lymphoid tissue atrophy in the thymus (females) 50 mg/kg: formation of cutaneous nodules (warts), high blood fibrinogen,[4)] low percentage of blood T cells/helper T cells/cytotoxic T cells, congestion of the spleen, subcutaneous papilloma (males and females); inanimation,[4)] lateral position,[4)] hunchback position,[4)] hyperthermia,[4)] mucous feces,[4)] diarrhea,[4)] dehydration,[4)] low blood leukocyte count, low blood lymphocyte count, low erythrocyte count, low hemoglobin, low erythrocyte distribution width, low hematocrit, low blood inorganic phosphate,[4)] testicular germ cell degeneration, increase in multinucleated giant spermatids in the testis, increase in epididymal cell debris, brown pigmentation in hepatic Kupffer cells, lymphoid tissue atrophy in the thymus, lymphoid tissue atrophy in mesenteric lymph nodes, decrease in lymphocytes in mesenteric lymph node sinuses, increased extramedullary hematopoiesis in the spleen (males) 20 mg/kg: reduced testicular size[4)] (males); high blood total bilirubin[4)] (females) With the exception of testicular toxicity-related findings, the findings were reversible for both filgotinib and GS-829845		
Male/ female dogs (beagle)	Oral gavage (filgotinib,GS-829845)	6 months (once daily)	Filgotinib 0, 2.5, 6/5,[a)] 15/7.5/10[b)] GS-829845 20/15,[c)] 40/20/30[d)]	**Filgotinib** <u>Dead animal[1)] (1 female)</u> 15/7.5/10 mg/kg: salivation,[2)] emaciation, oral mucosa/gum reddening, black discoloration of teeth, hunchback position, hyperthermia, inanimation, low blood leukocyte/neutrophil/eosinophil/lymphocyte count, low erythrocyte count, low hemoglobin/hematocrit, low blood ALP, high blood fibrinogen, brown areas/ulceration in the gums and tongue, lymphoid tissue atrophy in the thymus/spleen/GALT/mesenteric lymph nodes, vacuolated cells in gastric pits of the pyloric gland/in the gastric gland, necrotic cell debris within duodenal crypts, dilated duodenal crypts <u>Surviving animals</u> ≥2.5 mg/kg: decrease in germinal center cells of mesenteric lymph nodes/GALT (males); low eosinophil count (females) ≥6/5 mg/kg: nodules in the lips/ears/neck, vomiting, low blood basophil count, high blood APTT,[4)] depletion and increase in degeneration of testicular germ cells, decrease in epididymal sperm count, increase in epididymal cell debris, lymphoid tissue atrophy in mesenteric lymph nodes (males); increased salivation frequency,[2)] low blood lymphocyte count, low blood eosinophil count, low blood cytotoxic T cell count, low erythrocyte count, low hemoglobin/hematocrit, decrease in germinal center cells of mesenteric lymph nodes/GALT, increased extramedullary hematopoiesis in the spleen (females) 15/7.5/10 mg/kg: low blood leukocyte/T cell/helper T cell/activated T cell count (males and females); increased salivation frequency,[2)] low blood lymphocyte/eosinophil count, low erythrocyte count, low hemoglobin/hematocrit, low blood cytotoxic T cell/B cell count, low testicular weight, loss of germinal centers in mesenteric lymph nodes, increased extramedullary hematopoiesis in the spleen (males), hemorrhage/ulceration in the gums/lips, low blood basophil count, high blood APTT,[4)] lymphoid tissue atrophy in mesenteric lymph nodes (females) 6/5 mg/kg: ulceration in the foot, emaciation (females)	Filgotinib 2.5 (male) 10 (female) GS-829845 30	4.2.3.2.10

Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
				2.5 mg/kg: ulceration in the foot (males) **GS-829845** <u>Dead animals[1)] (2 males, 40 mg/kg)</u> 40 mg/kg: loose, watery red stool, emaciation, inanimation, black discoloration of teeth, ulceration in the gums, high body temperature, dehydration, pale skin, offensive odor, low hemoglobin/hematocrit, low blood lymphocyte count, abnormal electrolyte levels in blood, low blood protein, high blood fibrinogen/ALP, ulceration in the ileum and colon, necrotic cell debris in the small/large intestinal crypts, crypt hyperplasia in the small/large intestine, mixed inflammatory cell infiltration in the small/large intestine, fundic gland atrophy, dilated crypts and degeneration/necrosis in gastric pyloric gland, mixed inflammatory cell infiltration of the gall bladder mucosa, lymphoid tissue atrophy in the thymus/spleen/lymph nodes, GALT atrophy, dilatation of mesenteric lymph node sinuses, sinus erythrocytes, inflammatory cell infiltration <u>Surviving animals</u> ≥20/15 mg/kg: salivation,[2)] low blood lymphocyte count, decrease in germinal center cells of GALT, increased extramedullary hematopoiesis in the spleen (males and females); gum/lip hemorrhage, low blood basophil/T cell/helper T cell/cytotoxic T cell/activated T cell count, decrease in germinal center cells of mesenteric lymph nodes (males); ulceration in the foot, low blood eosinophil count (females) 40/20/30 mg/kg: lymphoid tissue atrophy in mesenteric lymph nodes (males and females); black discoloration of teeth, low blood eosinophil count, low erythrocyte count, low hemoglobin/hematocrit, loss of germinal centers in mesenteric lymph nodes (males); lip/gum ulcers, emaciation, low blood T cell/helper T cell/activated T cell count, decrease in germinal center cells of mesenteric lymph nodes (females) 20/15 mg/kg: nodules in the lips/ears/neck, ulceration in the foot, emaciation (males); black discoloration of teeth (females)		
Male/ female dogs (beagle)	Oral gavage (filgotinib, GS-829845)	9 months (once daily)	Filgotinib 0, 2.5, 5, 10/7.5/10[e)] GS-829845 20/15,[f)] 40/20/30[g)]	**Filgotinib** ≥2.5 mg/kg: extramedullary hematopoiesis/brown pigmentation in the spleen (males and females); low blood lymphocyte count, loss of germinal centers in the spleen (females) ≥5 mg/kg: decrease in germinal center cells of mesenteric lymph nodes/GALT (males and females); low blood eosinophil count, testicular germ cell depletion/degeneration, loss of germinal centers in mesenteric lymph nodes/spleen (males); salivation[2)] (females) 10/7.5/10 mg/kg: low blood leukocyte/basophil count, high APTT,[4)] low blood T cell/helper T cell/cytotoxic T cell/B cell count, GALT lymphoid tissue atrophy, skin inflammation/ulceration, brown pigmentation in hepatic Kupffer cells (males and females); salivation,[2)] low blood lymphocyte count, low percentage of motile sperm, low mean sperm count in semen, low testicular weight, decrease in epididymal sperm count, increase in epididymal cell debris, lymphoid tissue atrophy in mesenteric lymph nodes/the thymus, skin lesion associated with demodex infection, skin ulceration/granuloma/hyperkeratosis, thickening of the epidermis (males); low blood eosinophil count, low blood activated T cell count (females) 5 mg/kg: lymphoid tissue atrophy in mesenteric lymph nodes (females) 2.5 mg/kg: skin lesion associated with demodex infection, skin inflammation/granuloma (males) **GS-829845** <u>Dead animals[1)] (2 males, 40 mg/kg)</u> 40 mg/kg: sacrificed moribund because of serious skin lesion caused by infestation with demodex	Filgotinib 5 (male) 10 (female) GS-829845 15 (male) 30 (female)	4.2.3.2.11

Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
				Surviving animals ≥20/15 mg/kg: low blood lymphocyte count, loss of germinal centers in the spleen, brown pigmentation in the spleen (males and females); low blood eosinophil/helper T cell count, brown pigmentation in hepatic Kupffer cells, skin granuloma (males); salivation,[2)] low blood activated T cell count, decrease in germinal center cells of mesenteric lymph nodes/GALT, increased extramedullary hematopoiesis in the spleen (females) 40/20/30 mg/kg: low blood basophil count, lymphoid tissue atrophy in mesenteric lymph nodes, skin demodex infection/inflammation/ulceration (males and females); decrease in germinal center cells of mesenteric lymph nodes/GALT, hyperkeratosis, thickening of the epidermis, increased extramedullary hematopoiesis in the spleen (males); low blood T cell/helper T cell/cytotoxic T cell count, GALT lymphoid tissue atrophy (females)		
Male dogs (beagle)	Oral gavage (filgotinib)	39 weeks (once daily)	0, 3.7[h)]	None	—	4.2.3.2.14

Vehicle, a mixture of PEG400 and 30% (w/v) HPBCD aqueous solution (20/80, v/v)
a) 6 mg/kg (Week 1-); 5 mg/kg (Week 12-);
b) 15 mg/kg (Week 1-); 7.5 mg/kg (Week 6- in males; Week 7- in females); 10 mg/kg (Week 12-);
c) 20 mg/kg (Week 1-); 15 mg/kg (Week 12-);
d) 40 mg/kg (Week 1-); 20 mg/kg (Week 6- in males; Week 7- in females); 30 mg/kg (Week 12-);
e) 10 mg/kg (Week 1-); 7.5 mg/kg (Week 5- in males; Week 6- in females); 10 mg/kg (Week 12-);
f) 20 mg/kg (Week 1-); 15 mg/kg (Week 12-);
g) 40 mg/kg (Week 1-); 20 mg/kg (Week 5- in males; Week 6- in females); 30 mg/kg (Week 12-);
h) The initial dose level is shown. The dose level was adjusted at Weeks 3, 9, and 14 to maintain filgotinib $AUC_{0\text{-}24h}$ of 9 to 11 μg·h/mL.
1) Findings listed for dead animals are those that were considered to be associated with the test article.
2) The finding can be attributed to the oral gavage procedure, as well as to the unpalatable/texture of the liquid agent, and was assessed to be of low toxicological significance.
3) Abnormal testicular findings for the 2.5 mg/kg group were considered to have occurred spontaneously, and were thus not classified as toxicity.
4) The findings are assessed to be of low toxicological significance for reasons including the following: changes are within the range of historical control data at the laboratory or transient in nature, or absence of related abnormal/toxicological findings.

5.3 Genotoxicity

Genotoxicity studies consisted of *in vitro* bacterial reverse mutation assays (Ames tests), *in vitro* chromosome aberration study in mouse lymphoma cells, and *in vivo* rat bone marrow micronucleus assays (Table 19). The results demonstrated that filgotinib is not genotoxic. In the micronucleus study in rats (CTD 4.2.3.3.2.1), a significant increase in micronucleated polychromatic erythrocytes occurred at 2,000 mg/kg. However, given that the toxicity was observed at the excessive dose level only, at which a death occurred, the finding was assessed to be of low toxicological significance.

Table 19. Summary of genotoxicity studies

Test type		Test system	Metabolic activation (treatment duration)	Filgotinib concentration/dose	Test result	CTD
In vitro	Ames test	*Salmonella* ser. Typhimurium strains: TA98, TA100, TA1535, TA1537, TA102	S9 −/+	0, 52, 164, 512, 1,600, 5,000 μg/plate 0, 110, 197, 351, 627, 1,120, 2,000 μg/plate	Negative	4.2.3.3.1.1
	Chromosome aberration study in mouse lymphoma cells	Mouse lymphoma cells (L5178Y)	S9 − (24 hours)	0, 0.16, 0.51, 1.6, 5.1, 16, 51, 160, 500 μg/mL	Negative	4.2.3.3.1.2
			S9 − (4 hours)	0, 4.4, 7.8, 14, 25, 44, 78, 140, 250 μg/mL 0, 49, 88, 157, 280, 500 μg/mL		
			S9 + (4 hours)	0, 1.7, 3, 5.3, 9.5, 17, 31, 56, 100 μg/mL 0, 49, 88, 157, 280, 500 μg/mL		
In vivo	Rat micronucleus assay	Male and female rats (SD) bone marrow		0, 5, 15, 45 mg/kg/day (oral, 4-week repeated dose)	Negative	4.2.3.2.3
		Male rats (Wister) bone marrow		0, 500, 1,000, 2,000 mg/kg (oral, single dose)		4.2.3.3.2.1

DMSO (*in vitro*) or 0.5% MC aqueous solution (*in vivo*) was used as the vehicle.

5.4 Carcinogenicity

A 26-week mouse study was conducted to evaluate the carcinogenicity of filgotinib and GS-829845 administered orally to transgenic CByB6F1/Tg rasH2 (Tg rasH2) mice (Table 20). No filgotinib-related neoplastic lesions were noted [for evaluation of carcinogenicity, see Section 5.R.2]. Harderian gland adenoma and forestomach squamous cell carcinoma were observed in the filgotinib-treated mice but not in vehicle-treated mice, and angiosarcoma occurred at a higher frequency than the vehicle. However, it was concluded that these findings were unlikely to be related to filgotinib treatment because the data are within the range of historical control data for the animal models. Other non-proliferative lesions include atrophy/degeneration of seminiferous tubules in the testis. No new carcinogenic or systemic toxicities were identified for GS-829845 other than those observed for filgotinib.

The above determined that the non-carcinogenic dose for filgotinib was 150 mg/kg/day. The filgotinib $AUC_{0\text{-}24h}$ at Week 26 following repeated-dose administration at this dose level was 55.3 µg·h/mL for males and 61.9 µg·h/mL for females, corresponding to approximately 12.4-fold (males) and 13.9-fold (females), respectively, to the clinical exposure[11)] (AUC_{tau}, 4.45 µg·h/mL).

Table 20. Summary of the carcinogenic study using transgenic Tg rasH2 mice

Test system	Route of administration (Agent)	Dosing duration	Major lesion	Sex	Dose (mg/kg/day)						Non-carcinogenic dose (mg/kg/day)	CTD
					Vehicle	Filgotinib			GS-829845			
					0	15	50	150	150	500		
				N	25/sex	M, 25 F, 26	25/sex	25/sex	25/sex	25/sex		
Male/ female mice (Tg rasH2)	Oral gavage (Filgotinib, GS-829845)	26 weeks	Neoplastic lesions								Filgotinib 150 GS-829845 500	4.2.3.4.1.2
			Malignant lymphoma	M	1	0	1	0	0	0		
				F	0	1	0	0	0	0		
			Testis: Leydig cell tumor	M	0	0	0	0	0	0		
				F	—	—	—	—	—	—		
			Lung: bronchioloalveolar adenoma	M	1	0	0	0	0	0		
				F	1	1	0	0	1	0		
			Systemic: angiosarcoma	M	2	0	1	2	5	0		
				F	1	1	1	2	3	0		
			Harderian gland: adenoma/ adenocarcinoma	M	0	0	1	1	0	0		
				F	0	1	0	0	0	1		
			Proliferative lesions									
			Uterus: angiogenesis	M	—	—	—	—	—	—		
				F	0	0	0	1	0	0		
			Lung: bronchioloalveolar hyperplasia	M	1	0	0	0	2	0		
				F	0	0	1	1	0	0		
			Other findings									
			Survival (%)	M	96	96	96	100	96	96		
				F	100	96	100	100	96	100		
			Filgotinib 150 mg/kg/day: low testicular weight, testicular degeneration/atrophy, epididymal cell debris (males) **GS-829845** None									
			Vehicle, 0.5% MC aqueous solution									

A 2-year rat study was conducted to evaluate the carcinogenicity of filgotinib and GS-829845 administered orally (Table 21). Increased incidence and early onset of Leydig cell tumor (adenoma), one of the major neoplastic lesions associated with filgotinib treatment, were observed at 45 mg/kg. In addition, the following neoplastic lesions that occurred in the filgotinib/GS-829845 groups were not reported in the vehicle group:

amphophilic vacuolated renal tubule carcinoma in the filgotinib and GS-829845 groups, ovarian fibrosarcoma and squamous papilloma of the tongue in the filgotinib 45 mg/kg group, clitoral gland adenoma in the GS-829845 group. However, it was concluded that all of these findings were unlikely to be related to the test article based on various factors including the historical control data for the animal models and the statistical evaluation that took the dose and days to death into account.

Non-proliferative lesions were primarily as follows: atrophy/degeneration of seminiferous tubules in the testis; decrease in epididymal sperm count, exfoliated cells, and other changes in the epididymis; brown pigmentation in hepatic Kupffer cells, spleen, mandibular lymph nodes, and renal tubules; and lymphoid tissue atrophy in the thymus and lymph nodes. Brown pigmentation was considered to be of low toxicological significance because of absence of related findings such as cell degeneration/necrosis/inflammation. No new carcinogenic toxicities were identified for GS-829845 other than those observed for filgotinib.

On the basis of the above, the non-carcinogenic dose for filgotinib was determined to be 15 mg/kg/day for males and 45 mg/kg/day for females. The filgotinib $AUC_{0\text{-}24h}$ at Week 26 following repeated-dose administration at this dose level was 7.22 µg·h/mL for males and 34.9 µg·h/mL for females, corresponding to approximately 1.6-fold (males) and 7.8-fold (females), respectively, to the clinical exposure[11)] (AUC_{tau}, 4.45 µg·h/mL).

Table 21. Summary of the rat carcinogenicity study

Test system	Route of administration (Agent)	Dosing duration	Major lesion	Sex	Dose (mg/kg)							Non-carcinogenic dose (mg/kg/day)	CTD
					Vehicle		Filgotinib			GS-829845			
					0	0	5	15	45	25	75		
				N	45/sex	45/sex	60/sex	60/sex	70/sex	60/sex	70/sex		
Male/ female rats (SD)	Oral gavage (Filgotinib, GS-829845)	2 years	Neoplastic lesions									Filgotinib 15 (male) 45 (female) GS-829845 75	4.2.3.4.1.1
			Testis: Leydig cell tumor	M	3	0	2	1	9*	4	3		
				F	—	—	—	—	—	—	—		
			Adrenal medulla: malignant pheochromocytoma	M	0	0	2	1	4	1	3		
				F	0	1	1	0	0	1	1		
			Kidney: amphophilic vacuolated renal tubule carcinoma	M	0	0	0	0	1	1	1		
				F	0	1	0	0	0	0	0		
			Pancreas: islet cell adenoma	M	0	2	4	5	4	1	2		
				F	0	0	1	2	1	0	2		
			Pancreas: islet cell adenocarcinoma	M	1	0	1	0	0	4	0		
				F	0	1	0	0	1	1	0		
			Systemic organs/tissues[1]: angiosarcoma	M	0	1	1	0	0	0	4		
				F	0	0	2	1	0	0	1		
			Malignant lymphoma	M	2	0	1	0	0	0	1		
				F	0	1	1	1	0	0	0		
			Mammary gland: adenocarcinoma	M	0	0	1	1	0	1	0		
				F	24	12	22	27	27	14	20		
			Mammary gland: fibroadenoma	M	0	0	0	0	0	0	0		
				F	22	18	29	27	28	32	18		
			Clitoral gland: adenoma/adenocarcinoma	M	—	—	—	—	—	—	—		
				F	0	0	0	0	0	2	2		
			Other findings										
			Survival (%)	M	40	36	48	45	40	38	50		
				F	29	38	35	30	43	33	40		
			Filgotinib ≥5 mg/kg: salivation,[2] low blood lymphocyte count, low blood leukocyte count (females) ≥15 mg/kg: salivation,[2] (males); lymphoid tissue atrophy in the thymus (females) 45 mg/kg: backflow of injected liquid, brown pigmentation in hepatic Kupffer cells (males and females); low body weight, low blood lymphocyte count, reduced testicular/epididymal size, degeneration/atrophy of seminiferous tubules in the testis, decrease in epididymal sperm count, epididymal exfoliated cells, brown pigmentation in the spleen, increase in sinus erythrocytes in mesenteric lymph nodes (males); chromodacryorrhea/pigmented nasal discharge, inanimation, soiled urogenital organ, brown pigmentation in mandibular lymph nodes, lymphoid tissue atrophy in mesenteric lymph nodes (females) **GS-829845** ≥25 mg/kg: backflow of injected liquid (males and females), salivation,[2] (males); low blood lymphocyte count, low blood leukocyte count (females) 75 mg/kg: increase in sinus erythrocytes in mesenteric lymph nodes (males and females); low blood lymphocyte count, low blood leukocyte count, brown pigmentation in renal tubules (males), salivation,[2] chromodacryorrhea, low body weight, lymphoid tissue atrophy in mesenteric lymph nodes (females)										

Vehicle, 0.5% MC aqueous solution; *, this has been determined to be related to filgotinib treatment.
1) The adipose tissue, mesenteric lymph nodes, skin, and spleen
2) The finding can be attributed to the oral gavage procedure, as well as to the unpalatable/texture of the liquid agent, and was assessed to be of low toxicological significance.

5.5 Reproductive and developmental toxicity

Studies of fertility and early embryonic development to implantation were conducted using male and female rats to evaluate the toxicity of filgotinib and GS-829845 administered orally (Table 22). Filgotinib-related effects on female fertility were observed during early embryonic development. When filgotinib 60 mg/kg was administered to male rats, decrease in fertility, testicular toxicity, and related abnormal findings were observed. Abnormal epididymal events in rats treated with filgotinib 30 mg/kg were not classified as toxicity because they were reversible and did not impact fertility. No new toxicities were identified for GS-829845 other than those observed for filgotinib.

The above determined that the NOAEL for male reproductive toxicity in rats was 30 mg/kg/day. In a repeated-dose toxicity study,[12)] following administration of filgotinib at the above dose level, the filgotinib $AUC_{0\text{-}24h}$ at Week 13 was approximately 3.6-fold the clinical exposure[11)] (AUC_{tau}, 4.45 µg·h/mL). The NOAEL for reproductive toxicity in female rats was determined to be 60 mg/kg/day. When filgotinib 15 mg/kg/day was administered to pregnant animals in the study of the effects on pre- and postnatal development, including maternal function in rats,[13)] the filgotinib $AUC_{0\text{-}24h}$ at 10 days postpartum was approximately 1.9-fold the clinical exposure[11)] (AUC_{tau}, 4.45 µg·h/mL). The NOAEL for testicular toxicity was determined to be 3.7 mg/kg/day based on the results from the 39-week repeated-dose toxicity study in dogs (CTD 4.2.3.2.14, see Section 5.2) as dogs are considered to be most susceptible to the testicular toxicity effects of filgotinib. The filgotinib $AUC_{0\text{-}24h}$ at the NOAEL was 12.1 µg h/mL, which corresponds to approximately 2.7-fold the clinical exposure[11)] (AUC_{tau}, 4.45 µg·h/mL).

[12)] A 3-month repeated-dose toxicity study in rats (CTD 4.2.3.2.7; see Section 5.2)
[13)] A study of the effect of filgotinib on pre- and postnatal development, including maternal function in rats (CTD 4.2.3.5.3.1, see Section 5.5)

Table 22. Summary of fertility and early embryonic development studies

Test type	Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
Fertility and early embryonic development to implantation	Female rats (SD)	Oral gavage (Filgotinib, GS-829845)	From 14 days prior to mating to gestational day 7 (once daily)	Filgotinib 0, 15, 30, 60 GS-829845 60, 180	**Filgotinib** Parent animals None Early embryonic development 60 mg/kg: high mean percentage of early and late resorptions, high mean percentage of post-implantation loss, low mean number of live fetuses **GS-829845** Parent animals None Early embryonic development 180 mg/kg: high mean percentage of early and late resorptions, high mean percentage of post-implantation loss, low mean number of live fetuses	Filgotinib Parent (general toxicity): 60 Parent (reproductive toxicity): 60 Early embryonic development: 30 GS-829845 Parent (general toxicity): 180 Parent (reproductive toxicity): 180 Early embryonic development: 60	4.2.3.5.1.1
	Male rats (SD)	Oral gavage (Filgotinib, GS-829845)	From 62 or 28 days[a)] prior to mating throughout the mating period (once daily)	Filgotinib 0, 15, 30, 60 GS-829845 60, 180	**Filgotinib** Parent animals ≥30 mg/kg: epididymal exfoliated cells/cell debris 60 mg/kg: low body weight, low conception rate, low testicular/epididymal/seminal vesicle weight, reduced testicular/epididymal size, atrophy/degeneration of seminiferous tubules in the testis, vacuolation of seminiferous tubules in the testis, Leydig cell hyperplasia, secondary reduction in semen/azoospermia in the epididymis, low percentage of motile sperm, low percentage of normal-shaped sperm, low epididymal sperm count, low number of testicular sperm heads, low daily sperm production, high blood FSH, low blood inhibin B Early embryonic development None **GS-829845** Parent animals ≥60 mg/kg: low seminal vesicle weight[1)] 180 mg/kg: low epididymal weight [1)] Early embryonic development None	Filgotinib Parent (general toxicity): 30 Parent (reproductive toxicity): 30 Early embryonic development: 30 GS-829845 Parent (general toxicity): 180 Parent (reproductive toxicity): 180 Early embryonic development: 180	4.2.3.5.1.2

Vehicle, 0.5% MC aqueous solution
a) Filgotinib, from 62 days prior to mating; GS-829845, from 28 days prior to mating
1) The findings are assessed to be of low toxicological significance because of the absence of related abnormal/toxicological findings, and other reasons.

Studies of embryo-fetal development were conducted in rats and New Zealand White (NZW) rabbits to evaluate the toxicity of filgotinib and GS-829845 administered orally (Table 23). Effects on embryo-fetal development in rats and rabbits include visceral (the eye, lung, cardiovascular, and brain) and skeletal (axial skeleton) malformations. No NOAEL was established either for filgotinib or GS-829845. No new toxicities were identified for GS-829845 other than those observed for filgotinib. At the lowest observed adverse effect level for embryo-fetal development (LOAEL; 25 mg/kg/day for rats, and 10 mg/kg/day for rabbits), the filgotinib $AUC_{0\text{-}24h}$ was 17.2 μg·h/mL for rats at gestational day 17 and 9.65 μg·h/mL for rabbits at gestational day 20, corresponding to approximately 3.9-fold (rats) and 2.2-fold (rabbits), respectively, to the clinical exposure[11)] (AUC_{tau}, 4.45 μg·h/mL).

Table 23. Summary of embryo-fetal development studies

Test type	Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
Embryo-fetal development	Female rats (SD)	Oral gavage (Filgotinib, GS-829845)	From gestational days 6-17 (once daily) Caesarean section: gestational day 20	Filgotinib 0, 25, 50, 100 GS-829845 60, 180	**Filgotinib** <u>Dams</u> 100 mg/kg: low body weight, low body weight gain corrected for uterus weight[1)] <u>Embryo-fetal development</u> ≥25 mg/kg: internal hydrocephalus,[2)] ureter dilatation[3)] vertebral abnormalities with/without rib anomalies,[2)] sternal abnormalities,[2)] defect between the first cervical vertebra and occipital bone,[2)] rib abnormalities,[2)] mild to moderate irregular arrangement of sternebrae ≥50 mg/kg: absent/small eyeballs,[2)] convoluted ureter variation,[3)] decreased vertebral ossification,[3)] unossified vertebrae[3)] 100 mg/kg: low number of live fetuses, high number of early and late resorptions, high number of total resorptions, high mean post-implantation loss, low fetal weight, absent lung lobes/lobulation anomaly/small lobulation of the lung,[2)] retroesophageal aortic arch,[2)] transposition of the great arteries,[2)] ventricular septum defect,[2)] abnormal position of the heart (right),[2)] right aortic arch,[2)] external hydrocephalus,[2)] brain malformation,[2)] thyroid gland deficiency,[2)] situs inversus viscerum,[2)] abnormal lobulation of the liver,[2)] absent renal papilla,[3)] pale spleen,[3)] aberrant right subclavian artery,[3)] short rib variation,[3)] unossified sternebrae,[3)] unossified middle finger bone/metatarsal bone,[3)] ossification variation in the first cervical vertebral body[3)] 25 and 50 mg/kg: short cervical rib in the 7th cervical vertebra,[3)] lower limb girdle cranial deviation[3)] 50 mg/kg: vertebral body abnormality,[2)] long cervical rib in the 7th cervical vertebra[3)] 25 mg/kg: curvature of the rib[3)] **GS-829845** <u>Dams</u> 180 mg/kg: low body weight, low body weight gain[4)] <u>Embryo-fetal development</u> ≥60 mg/kg: ureter dilatation,[3)] convoluted ureter variation,[3)] unossified sternebrae,[3)] curvature of the rib[3)] 180 mg/kg: excessive liver lobulation,[3)] curvature of limb bone[2)] <u>60 mg/kg: internal hydrocephalus[2)]</u>	Filgotinib Dams (general toxicity): 100 Embryo-fetal development: <25 GS-829845 Dams (general toxicity): 180 Embryo-fetal development: <60	4.2.3.5.2.2
	Female rabbits (NZW)	Oral gavage (Filgotinib, GS-829845)	From gestational days 7-20 (once daily) Caesarean section: gestational day 29	Filgotinib 0, 10, 25, 60 GS-829845 60, 150	**Filgotinib** <u>Dams</u> ≥25 mg/kg: decreased stool volume, low body weight, low food consumption 60 mg/kg: death, spontaneous abortion, coma, hunchback position, piloerection, emaciation, low body temperature, mild dehydration symptoms, prostration, ventrolateral recumbency, bradypnea, pallor, faded color stool, moribund state, bright red liquid within the cage <u>Embryo-fetal development</u> ≥10 mg/kg: fused sternebrae[2)] ≥25 mg/kg: vertebral abnormalities with/without rib anomalies,[2)] sternal abnormalities,[2)] costal cartilage abnormalities[2)] 60 mg/kg: low mean number of live fetuses, high mean post-implantation loss, low mean fetal weight, absent lung lobes/lobulation anomaly,[2)] ventricular septum defect,[2)] aortic	Filgotinib dams (general toxicity): 10 Embryo-fetal development: <10 GS-829845 dams (general toxicity): 60 Embryo-fetal development: <60	4.2.3.5.2.4

Test type	Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
					arch interruption[2)]/dilation,[2)] atrial enlargement,[2)] absence/reduced size of the gallbladder,[3)] pale spleen,[3)] aberrant right subclavian artery,[3)] rib abnormalities,[2)] defect between the first cervical vertebra and occipital bone,[2)] caudal vertebra abnormalities,[2)] sternal clefts,[2)] short cervical rib in the 7th cervical vertebra,[3)] long cervical rib in the 7th cervical vertebra,[3)] lower limb girdle cranial deviation,[3)] mild to moderate irregular arrangement of sternebrae,[3)] unossified 5th/6th pieces of the sternum,[3)] unossified tarsal bone,[3)] decreased ossification of the vertebral body,[3)] unossified middle finger bone/metatarsal bone,[3)] unossified pubic bone **GS-829845** <u>Dams</u> 150 mg/kg: decreased stool volume, coma, hunchback position, piloerection, emaciation, ventrolateral recumbency, bradypnea, pallor, faded color stool, moribund state, low body weight, low food consumption <u>Embryo-fetal development</u> ≥60 mg/kg: vertebral abnormalities with/without rib anomalies,[2)] fused sternebrae[2)] <u>180 mg/kg: high mean post-implantation loss</u>		

Vehicle, 0.5% MC aqueous solution
1) These effects are considered to be secondary to fetal toxicity of filgotinib; 2) malformations; 3) variations;
4) These findings are mild in degree and thus assessed to be of low toxicological significance.

A study of the effects on pre- and postnatal development, including maternal function was conducted using rats to evaluate the toxicity of filgotinib and GS-829845 administered orally (Table 24). No effects on maternal reproductive capacity or F_1 generation were noted. In GS-829845-treated rats, early preputial separation occurred, an event which was not noted in filgotinib-treated rats. However, given that the event was within the range of historical control data at the laboratory, and related abnormal findings were absent, the event was assessed to be of low toxicological significance. The NOAEL was determined to be 15 mg/kg/day for dams and pups. When repeated doses of filgotinib at the NOAEL were administered to dams, the filgotinib $AUC_{0\text{-}24h}$ at 10 days postpartum was 8.32 μg·h/mL, corresponding to approximately 1.9-fold the clinical exposure[11)] (AUC_{tau}, 4.45 μg·h/mL).

Table 24. Summary of the study of the effects on pre- and postnatal development, including maternal function

Test type	Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
Effects on pre- and postnatal development, including maternal function	Female rats (SD)	Oral gavage (Filgotinib, GS-829845)	Dams: From gestational day 6-20 days postpartum (once daily)	Filgotinib 0, 2, 5, 15 GS-829845 10, 30	**Filgotinib** Dams None F_1 offspring None F_2 offspring None **GS-829845** Dams None F_1 offspring ≥10 mg/kg: early preputial separation F_2 offspring None	Filgotinib Dams (general toxicity): 15 Dams (reproductive toxicity): 15 F_1 offspring (general toxicity): 15 F_1 offspring (reproductive toxicity): 15 F_2 offspring (toxicity): 15 GS-829845 Dams (general toxicity): 30 Dams (reproductive toxicity): 30 F_1 offspring (general toxicity): 30 F_1 offspring (reproductive toxicity): 30 F_2 offspring (toxicity): 30	4.2.3.5.3.1

Vehicle, 0.5% MC aqueous solution

5.6 Juvenile animal studies

Studies on the repeated oral dose toxicity of filgotinib and GS-829845 were conducted in juvenile rats (Table 25). Major toxicity findings of filgotinib included incomplete enamel formation in the incisor, testicular spermatogenesis failure, low blood leukocyte/lymphocyte parameters and low erythrocyte parameters. A high ALP level in blood was unique to juvenile animals. Decrease in bone marrow hematopoietic cellularity and low leukocyte/lymphocyte parameters are effects associated with the inhibition of JAKs by filgotinib and were reversible; therefore, these events were not considered to be toxicity findings. No new toxicities were identified for GS-829845 other than those observed for filgotinib.

On the basis of the above, the NOAEL in the juvenile rat 11-week repeated-dose toxicity study was determined to be 20 mg/kg/day. When filgotinib was administered in repeated doses at the NOAEL, $AUC_{0\text{-}24h}$ was 15.8 μg·h/mL (male/female combined) on postnatal days 91, corresponding to approximately 3.6-fold the clinical exposure[11)] (AUC_{tau}, 4.45 μg·h/mL).

Table 25. Summary of repeated-dose toxicity studies in juvenile animals

Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
Male/ female juvenile rats (SD)	Oral gavage (Filgotinib, GS-829845)	Postnatal days 22-45 (once daily)	Filgotinib 0,[a] 20, 60, 180 GS-829845 60, 180	**Filgotinib** ≥20 mg/kg: salivation,[1] (males and females); decrease in epididymal sperm volume[2] ≥60 mg/kg: reduced spleen size (males and females); loss/disruption of incisor ameloblasts, incomplete enamel formation in the incisor (males) 180 mg/kg: low blood leukocyte/eosinophil/basophil/lymphocyte count, low erythrocyte count, low hemoglobin/hematocrit, high MCV, whitened mandibular incisors, reduced thymus size (males and females); low body weight/body weight gain, hunchback position,[3] piloerection,[3] inanimation,[3] half-closed eyes,[3] emaciation,[3] low reticulocyte count, low testicular weight, reduced testicular size, reduced epididymal size, atrophy/degeneration of seminiferous tubules in the testis (males); high blood inorganic phosphate/triglyceride/ALP/total bilirubin[3] levels, low blood chloride/sodium levels, loss/disruption of incisor ameloblasts, incomplete enamel formation in the incisor (females) 20 and 60 mg/kg: decrease in elongated spermatids in the testis in Stage VII **GS-829845** ≥60 mg/kg: high blood ALP (males and females); low body weight/body weight gain, decrease in epididymal sperm volume[3] (males) 180 mg/kg: low blood leukocyte/neutrophil/basophil/lymphocyte count (males); high blood albumin (females)	Filgotinib 20 (male) 60 (female) GS-829845 60 (male) 180 (female)	4.2.3.5.4.1
Male/ female juvenile rats (SD)	Oral gavage (Filgotinib, GS-829845)	Postnatal day 14 to Week 11 (once daily)	Filgotinib 0,[b] 2, 6, 20 GS-829845 30, 90	**Filgotinib** ≥6 mg/kg: decrease in bone marrow hematopoietic cells (males) 20 mg/kg: low spleen weight, decrease in lymphocyte cellularity in the spleen (males and females); low blood lymphocyte/leukocyte/T lymphocyte/helper T cell/cytotoxic T cell count, decrease in bone marrow hematopoietic cells (females) **GS-829845** ≥30 mg/kg: decrease in bone marrow hematopoietic cells (males); low blood lymphocyte/leukocyte/T lymphocyte/helper T cell/cytotoxic T cell count, low spleen weight (females) 90 mg/kg: decrease in lymphocyte cellularity in the spleen (males and females); low spleen weight (males); low blood NK cell count, decrease in bone marrow hematopoietic cells (females)	Filgotinib 20 GS-829845 90	4.2.3.5.4.2

a) 0.5% MC aqueous solution
b) 0.5% MC aqueous solution or 0.5% HPMC/0.2% polysorbate 80 aqueous solution
1) The event can be attributed to the oral gavage procedure, as well as to the unpalatable/texture of the liquid agent, and was assessed to be of low toxicological significance.
2) The findings at 20 and 60 mg/kg were not classified as toxicity events.
3) It is considered that the events are of low toxicological significance because of the transient nature of the changes, absence of related abnormal/toxicological findings, and other reasons.

5.7 Local tolerance

A skin corrosion study was conducted using an *in vitro* model, and the results showed that filgotinib is non-corrosive (Table 26). A bovine corneal opacity and permeability (BCOP) assay was conducted to evaluate ocular irritation. Under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), filgotinib is classified as mild irritant and "no prediction" can be made (Table 26).

Table 26. Summary of local tolerance studies of filgotinib

Test type	Test system	Test method	Major findings	CTD
Skin corrosion test	EpiSkin®	After applying 20 mg onto the surface, cell viability was evaluated 3 minutes, 1 hour, and 4 hours later	Viability, 99.3% (3 minutes later), 100.9% (1 hour later), and 98.5% (4 hours later) The result indicated that filgotinib is non-corrosive.	4.2.3.6.1
BCOP assay	Isolated bovine cornea	After 20% solution was added, permeability was assessed 90 minutes, and opacity was assessed 4 hours later	Irritancy score, 10.88 GHS classification, no prediction; filgotinib is classified as mild irritant.	4.2.3.6.2

5.8 Other studies

5.8.1 Skin sensitization

A local lymph node assay (LLNA) was conducted, and filgotinib was not considered to be a skin sensitizer (Table 27).

Table 27. Summary of skin sensitization study of filgotinib

Test type	Test system	Test method	Major findings	CTD
LLNA	Female mice (CBA/J)	0.01%, 0.02%, and 0.05% solution and vehicle control (DMSO) were applied onto the back of both auricles once daily for 3 days	None Not considered to be a skin sensitizer	4.2.3.7.1.1

5.8.2 Phototoxicity

In neutral red uptake (NRU) mouse fibroblast assays to evaluate phototoxicity, it was shown that filgotinib was potentially phototoxic. In a phototoxicity study in pigmented rats, neither filgotinib or GS-829845 exhibited abnormal findings to the eye, eyelids, or skin, and therefore both filgotinib and GS-829845 were not considered to be phototoxic (Table 28).

Table 28. Summary of phototoxicity studies

Test type	Test system	Test method	Major findings	CTD
Phototoxicity	Mouse fibroblasts (BALB/c 3T3)	0,[a] 67.42, 99.11, 145.69, 214.16, 314.81, 462.77, 680.27, 1,000 µg/mL UV-A 5 J/cm^2 irradiation	Potentially phototoxic (photo irritant factor of 2.9; mean photo effect of 0.12)	4.2.3.6.3
	Female pigmented rats (Long-Evans)	Filgotinib: 0,[b] 30, 60, 180 mg/kg GS-829845: 60, 360 mg/kg Oral gavage, once daily for 3 days. UV-A (10 J/cm^2, approximately 60 min.) and UV-B (0.1 J/cm^2, approximately 80 sec.) irradiated immediately after administration	Not phototoxic	4.2.3.6.4

a) PBS solution containing 1% DMSO; b) 0.5% MC aqueous solution

5.8.3 Immunotoxicity

No immunotoxicity studies with filgotinib or GS-829845 were performed. In the repeated-dose toxicity studies in rats and dogs, decreases in blood leukocyte, T cell, and NK cell counts, decrease in cellularity or lymphocyte depletion in lymphoid tissues occurred. In the 9-month repeated-dose toxicity study in dogs, findings including increased susceptibility to parasitic infection and cutaneous lesions associated with reactivation of canine papillomavirus infections were observed [see Section 5.2].

5.8.4 Mechanistic study on toxicity

5.8.4.1 Exploratory study to investigate rat testicular toxicity

A rat mechanistic study was conducted to investigate the testicular toxicity of filgotinib (Table 29). Filgotinib did not affect blood testosterone or follicle stimulating hormone (FSH) levels. While the blood inhibin B levels tended to increase after administration of filgotinib, no change in the gene expression of inhibin B was observed

in the gene expression analysis, indicating no effect of filgotinib under the testing conditions. The gene expression profiling analysis using RNA extracted from the testes showed that filgotinib did not affect the transcription of genes relevant to the JAK pathway in the testis and, furthermore, the gene expression observed did not match any profile within public databases. The findings suggest that the testicular toxicity of filgotinib may represent a novel mechanism, unrelated to JAK inhibition.

Table 29. Summary of the rat exploratory study on the testicular toxicity of filgotinib

Test type	Test system	Test method	Major findings	CTD
Mechanistic study on testicular toxicity	Male rats (SD)	Filgotinib 0,[a] 45, or 180 mg/kg was administered by oral gavage once daily for up to 7 days (1, 3, or 7 days) Measurement of blood testosterone, FSH, and inhibin B levels; histopathological study of male reproductive organs (the testis, epididymis, prostate, seminal vesicle, and coagulating gland); gene expression profiling analysis using RNA extracted from the testis	180 mg/kg: observed trend towards increased inhibin B, low seminal vesicle/testis/epididymis weight, gene expression changes (4 hours post-dose); no changes in genes related to the JAK pathway (target pathway), the gene expression observed did not match any profile in existing databases	4.2.3.7.3.1

a) 0.5% MC aqueous solution

5.8.5 Toxicity evaluation of metabolite

The systemic toxicity, carcinogenicity, reproductive toxicity, and *in vivo* phototoxicity of GS-829845, the major human metabolite of filgotinib, were evaluated based on data from the GS-829845 groups established in each toxicity study of filgotinib [see Sections 5.2, 5.4, 5.5, 5.6, and 5.8.2]. Additionally, a genotoxicity study and an *in vitro* phototoxicity study were performed for GS-829845. No new toxicities were identified other than those observed for filgotinib in any of the toxicity studies.

5.8.5.1 Genotoxicity

Genotoxicity studies consisted of Ames tests, a chromosome aberration study in mouse lymphoma cells, and rat bone marrow micronucleus assays (Table 30). GS-829845 was not considered to be genotoxic based on the results.

Table 30. Summary of genotoxicity studies on GS-829845

Test type		Test system	Metabolic activation (treatment duration)	Concentration/dose	Test result	CTD
In vitro	Ames test	*Salmonella* ser. Typhimurium strains: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP 2*uvrA*	S9 −/+	0,[a] 100, 333, 1,000, 3,330, 5,000 µg/plate	Negative	4.2.3.7.5.1
	Chromosome aberration study in mouse lymphoma cells	Mouse lymphoma cells (L5178Y)	S9 − (24 hours)	0,[a] 3, 10, 33, 50, 70, 90, 100, 125 µg/mL	Negative	4.2.3.7.5.4
			S9 − (3 hours)	0,[a] 0.1, 0.3, 1, 3, 10, 33, 100, 357 µg/mL		
			S9 + (3 hours)	0,[a] 0.1, 0.3, 1, 3, 10, 33, 100, 357 µg/mL		
In vivo	Rat micronucleus assay	Male rats (SD) Bone marrow		0,[b] 500, 1,000, 2,000 mg/kg/day (oral, in 2 doses, 24 hours apart)	Negative	4.2.3.7.5.6

a) DMSO; b) 0.5% MC aqueous solution

5.8.5.2 Phototoxicity

NRU mouse fibroblast assays were performed to evaluate phototoxicity, and the results indicated that GS-829845 was potentially phototoxic (Table 31). In a phototoxicity study in pigmented rats, it was shown that GS-829845 was not phototoxic (Table 28).

Table 31. Summary of phototoxicity study on GS-829845

Test type	Test system	Test method	Major findings	CTD
Phototoxicity	Mouse fibroblasts (BALB/c 3T3)	0,[a] 4.71, 10.13, 21.77, 46.80, 100.62, 216.33, 465.12, 1,000 μg/mL UV-A 5 J/cm^2 irradiation	Potentially phototoxic (photo irritant factor >24.58; mean photo effect of 0.50)	4.2.3.7.5.7

a) PBS solution containing 1% DMSO

5.8.6 Impurities

GS-829845, Impurity 4, Impurity 5, Impurity 6, and Impurity 1 were identified impurities in the proposed manufacturing process for the drug substance. The identified impurities, except for the major metabolite GS-829845, were assessed for mutagenicity by a quantitative structure-activity relationship analysis, or (Q)SAR analysis, and Impurity 4 and Impurity 5 tested negative. While the (Q)SAR analysis failed to rule out mutagenicity of Impurity 6 and Impurity 1, the results of the Ames assays (CTD 4.2.3.7.6.6 and 4.2.3.7.6.8) showed that both of the impurities were negative for mutagenicity. A rat repeated-dose toxicity study was conducted using a high purity drug substance and low purity drug substance containing filgotinib-related process impurities (Table 32). No toxicologically significant differences between batches were noted.

Potential impurities that could be generated during the manufacture of the drug substance were investigated. Impurity D2 and Impurity D1 were identified as being or expected to be mutagenic. However, given that the human exposure is to be kept below the toxicological threshold for potentially mutagenic impurities through the management of the starting materials and elimination from the manufacturing process in the subsequent steps, the impurities were unlikely to be a safety concern.

Table 32. Summary of the repeated oral-dose toxicity study with drug substances containing impurities

Test system	Route of administration (Agent)	Dosing duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	CTD
Male/female rats (SD)	Oral gavage (Drug substances containing filgotinib-related impurities)	4 weeks (once daily)	Test article 1[a]: 45 Test article 2[b]: 20, 45 Vehicle[c]: 0	**Test Article 1** 45 mg/kg: low blood lymphocyte/leukocyte count, decrease in bone marrow hematopoietic cells, low spleen/thymus weight, increase in bone marrow adipose tissues (males and females); low large unstained cell count in blood, low neutrophil count (females) **Test Article 2** ≥20 mg/kg: low blood lymphocyte/leukocyte count, increase in bone marrow adipose tissues (males and females); low large unstained cell count in blood, low thymus/spleen weight (females) 45 mg/kg: low large unstained cell count in blood, low pituitary/seminal vesicle/spleen/ thymus weight (males); low neutrophil count (females)	Test Article 1: 45 Test Article 2: 45	4.2.3.7.6.13

a) Filgotinib (Batch No. [redacted] [purity [redacted]%])
b) Filgotinib (Batch No. [redacted] [purity [redacted]%])
c) 0.5% HPMC/0.2% polysorbate 80 aqueous solution

5.R Outline of the review conducted by PMDA

5.R.1 Systemic toxicity

5.R.1.1 Effects on the immune system

The applicant's explanation about the effects of filgotinib on the immune system:

Effects of filgotinib on the immune system include JAK inhibition-related effects, primarily decreases in leukocyte, T lymphocyte, and NK cell counts, decreases in lymphocyte cellularity in lymphoid tissues, as well as increased susceptibility to parasitic infection and reactivation of canine papillomavirus infections; however, these events were reversible after a recovery period.

PMDA's view on the immunosuppressive effects of filgotinib as a JAK inhibitor:
In the dog repeated-dose toxicity study, findings suggestive of immunosuppression, i.e., increased susceptibility to parasitic infection, and of reactivation of canine papillomavirus infections were observed. This requires thorough discussion based on the results from clinical studies to address the risk for development of infections caused by the immunosuppressive effects of filgotinib and the safety of filgotinib in patients who have already contracted certain infectious diseases [see Section 7.R.3].

5.R.1.2 Effects on erythrocyte parameters

The applicant's explanation:
In the repeated-dose toxicity studies in rats and dogs, a trend towards decreased erythrocyte parameters, increased hematopoiesis and decrease in bone marrow cellularity, and brown pigmentation suggestive of hemosiderin or lipofuscin deposition in the liver, spleen, kidney, and lymph nodes were observed. Similar findings were reported for previously approved JAK inhibitors, e.g., tofacitinib, baricitinib, and upadacitinib (see "Review Report of Xeljanz Tablets 5 mg," dated February 28, 2013, "Review Report of Olumiant Tablets 2 mg and 4 mg," dated May 19, 2017, and "Review Report of Rinvoq Tablets 7.5 mg and 15 mg," dated November 14, 2019). While these findings are likely to be the effects of enhanced erythrocyte metabolic turnover/extracellular destruction associated with JAK2 inhibition, the events are unlikely to raise safety concerns in the clinical use of filgotinib because of a sufficient safety margin compared to the clinical exposures, and absence of hypoxia-related toxicity findings.

PMDA's view:
The effects on erythrocyte parameters observed in the non-clinical studies were abnormal findings related to JAK inhibition. This requires thorough discussion based on the results from clinical studies to address the safety of filgotinib in humans [see Section 7.R.3].

5.R.2 Carcinogenicity

The applicant's explanation about the mechanism of increased incidence and early onset of benign Leydig cell hyperplasia/adenoma in filgotinib-treated rats in the rat carcinogenicity study:
The factors shown below suggest that these events are unlikely to pose significant risk in the clinical use of filgotinib. Information on the toxicity findings from the non-clinical studies, albeit their clinical implications remain unclear, will be provided in the package insert.

- Studies have suggested that elevated LH levels in blood may be linked to increase in Leydig cell hyperplasia/tumor proliferation in rats (*Crit Rev Toxicol.* 1999;29:169-261). Increased incidence of benign Leydig cell tumors has been reported at elevated blood LH levels in a number of rat carcinogenicity studies of the following drugs: lansoprazole (*Fundam Appl Toxicol*. 1995;26:191-202), procymidone (*Toxicol*

Appl Pharmacol. 1995;131:244-52), mesulergine (*Arch Toxicol Suppl.* 1992;197-204), SDZ 200-110 (*J Amer Coll Toxicol.* 1989;8:487-505), flutamide (*Acta Endocrinol.* 1983;104:246-52), and canagliflozin (*Chem Biol Interact.* 2014;224:1-12). When repeated doses of filgotinib were administered to rats, blood LH levels increased to similar level as the drugs shown above, suggesting that increase in blood LH levels is also involved in increased incidence of filgotinib-induced benign Leydig cell tumors.

- In the rat carcinogenicity study of tofacitinib, there was an increase in the incidence of benign Leydig cell tumors, which was related to a mechanism involving elevated LH levels resulting from a decline in blood prolactin levels caused by JAK2 inhibition (*Toxicol Sci*. 2017;155:148-56); however, when repeated doses of filgotinib were administered to rats, no effects on prolactin secretion were observed. Therefore, involvement of JAK inhibition-induced decline in prolactin secretion is unlikely, and low testosterone levels related to testicular toxicity [see Section 5.R.3.1] may be involved.
- It has been reported that Leydig cells in rats have more LH receptors and have a higher LH sensitivity than those in humans (*Crit Rev Toxicol.* 1999;29:169-261). No adverse events suggestive of filgotinib-induced elevation of blood LH levels were noted in any of the filgotinib clinical studies.

PMDA accepted the applicant's explanation.

5.R.3 Reproductive development toxicity

5.R.3.1 Effects on male reproductive organs

The applicant's explanation about the testicular toxicity findings observed in rats and dogs and safety in humans:

The factors shown below suggest that potential of filgotinib to affect human spermatogenesis and fertility has not been clarified; however, information on the toxicity findings from the non-clinical studies will be provided in the package insert.

- The gene expression analysis using the testes exhibiting abnormalities following administration of filgotinib showed that filgotinib-induced JAK/STAT pathway inhibition was not observed in the testis. Furthermore, testicular toxicity findings were not observed in non-clinical studies of other JAK inhibitors (see "Review Report of Xeljanz Tablets 5 mg," dated February 28, 2013, "Review Report of Olumiant Tablets 2 mg and 4 mg," dated May 19, 2017, "Review Report of Rinvoq Tablets 7.5 mg and 15 mg," dated November 14, 2019), suggesting that testicular toxicity is likely to be associated with the off-target effects of filgotinib; however, the detailed mechanism is unknown at present.
- In clinical studies, incidence of male reproductive adverse events was low and no clinically significant changes in the secretion of male reproductive hormones (i.e., testosterone, FSH, LH, prolactin, and inhibin B) were observed [see Section 7.R.3.2]. A foreign clinical study evaluating the testicular effect of filgotinib is currently ongoing; the potential risk for humans is unknown at present.

PMDA's view:

There is a safety concern over the testicular toxicity of filgotinib in humans for the following reasons: currently, the mechanism of testicular toxicity associated with filgotinib treatment has not been clarified; the same findings have been observed both in rodents and non-rodents; the exposure safety margin between the clinical

and non-clinical doses is small; and the reversibility of some of the findings in dogs is low. Therefore, thorough consideration will be necessary taking into account of safety and efficacy data from clinical studies regarding the use of filgotinib in men such as restricting use to only when the benefits outweigh the risk of testicular toxicity [see Section 7.R.3.2].

Following repeated-dose administration to juvenile rats, or administration of filgotinib to sexually immature beagle dogs, testicular toxicity requiring a prolonged recovery period has been reported. When clinical development is conducted for the intended population that includes young male children to young adult males who have reached sexual maturity, a thorough discussion will be required on the safety of the reproductive function after secondary sexual characteristics have developed.

5.R.3.2 Effects on embryos, fetuses, and live-born offspring

The applicant's explanation about the safety in humans in terms of the effects on early embryonic development, embryos, fetuses, and live-born offspring:

- Similar teratogenicity findings in rat and rabbit fetuses, namely, visceral and skeletal abnormalities, were reported with other JAK inhibitors (see "Review Report of Xeljanz Tablets 5 mg," dated February 28, 2013, "Review Report of Olumiant Tablets 2 mg and 4 mg," dated May 19, 2017, "Review Report of Rinvoq Tablets 7.5 mg and 15 mg," dated November 14, 2019), and such teratogenic effects are likely to be caused by JAK inhibition. Therefore, filgotinib should be contraindicated in women who are or may be pregnant, and effective contraception should be practiced by women of childbearing potential during treatment and for a certain period after the end of treatment with filgotinib. The above caution statement will be provided in the package insert.
- No particular effects were noted in rat pups breast-fed by dams treated with filgotinib; however, filgotinib was detected in the plasma of breast-fed pups, likely through breast milk [see Section 4.4.2]. Because it is evident that filgotinib is transferred from the dam to the pup via breast milk, filgotinib should be discontinued during breast-feeding, and caution statement will be provided in the package insert.

PMDA accepted the applicant's explanation.

5.R.4 Effects on dental development

The applicant's explanation about degeneration and necrosis of ameloblasts and incomplete enamel formation in rat incisors, and safety in humans:

- The findings in rats indicated that ameloblasts are susceptible to filgotinib in the secretory stage and maturation stage, suggesting that filgotinib may cause enamel dysplasia such as enamel hypoplasia or hypocalcification in humans. The possibility that filgotinib has potential risks that could affect permanent tooth development in humans, specifically, late stage of tooth morphogenesis and crown morphogenesis cannot be ruled out (*J Exp Zool B Mol Dev Evol.* 2009;312B:437-44).
- The NOAEL for toxic effects on incisors is 20 mg/kg/day for both juvenile rats and mature rats. The filgotinib $AUC_{0\text{-}24h}$ (male/female combined) at this dose level was 15.8 μg·h/mL for juvenile rats and 19.9 μg·h/mL for mature rats, corresponding to approximately 3.6-fold and 4.5-fold, respectively, to the

clinical exposure[11] (AUC_{tau}, 4.45 μg·h/mL). There was no trend towards an increase in sensitivity in terms of toxic effects on the incisor in juvenile animals compared to mature animals.

Taking into account that permanent tooth morphogenesis in humans begins after birth (*Wheeler's Dental Anatomy, Physiology, and Occlusion.* 2003:32), the effects are unlikely to raise safety concerns in adults because the development of permanent teeth has already been completed. However, when clinical development is conducted for the intended population including pediatric patients, in whom permanent tooth development has not been completed, safety needs to be thoroughly considered.

5.R.5 Effects on bone

The applicant's explanation of the results from the repeated-dose toxicity study in juvenile rats indicated that filgotinib had no effects on the femur, and is unlikely to raise safety concerns over bone growth.

PMDA's view on the effects on bone:

On the basis of the following toxicity findings, systemic JAK-STAT signaling inhibition may affect bone development and growth: fetal skeletal abnormalities were reported in non-clinical studies of filgotinib and other JAK inhibitors (see "Review Report of Xeljanz Tablets 5 mg," dated February 28, 2013, "Review Report of Olumiant Tablets 2 mg and 4 mg," dated May 19, 2017, "Review Report of Smyraf Tablets 50 mg and 100 mg," dated May 31, 2019), and necrotic changes and other anomalies in the femoral metaphysis were reported in the repeated-dose toxicity study of peficitinib in mature rats (see "Review Report of Smyraf Tablets 50 mg and 100 mg," dated May 31, 2019). While the effects may be insignificant in adults who have already reached bone maturation, when clinical development is conducted for the intended population that includes pediatric patients who are at the stage of rapid bone growth, safety needs to be thoroughly considered.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Biopharmaceutic evaluation data including results from relative bioavailability studies were submitted.

In the clinical development of filgotinib, mainly 4 types of formulations were used[14]: Formulation 1 (filgotinib [redacted], oral solution), Formulation 2 (filgotinib [redacted], capsules: 10, 25, 50, and 100 mg), Formulation 3 (filgotinib [redacted], film-coated tablets: 25 and 100 mg), and Formulation 4 (filgotinib maleate, film-coated tablets: 100 and 200 mg). Formulation 4 is the proposed commercial formulation. The relative bioavailability of the formulations was evaluated in Study GLPG0634-CL-107 (Formulations 2 and 3) and in Study GS-US-417-3900 (Formulations 3 and 4). The results from *in vitro* dissolution testing demonstrated equivalence with

[14] Different formulations were used in the clinical studies: Formulation 1 in phase I study (Study GLPG0634-CL-101); Formulation 2 in phase I studies (Studies GLPG0634-CL-101, -102, -103, -104, and -107), and phase II studies (Studies GLPG0634-CL-201, -202, -203, -204, and -205); Formulation 3 in phase I studies (Studies GLPG0634-CL-106, -107, -110, and GS-US-417-3900), and phase II studies (Studies GLPG0634-CL-205 and -211); Formulation 4 in phase I studies (Studies GS-US-417-3900, -3911, -3916, -4048, and -4107), phase II studies (Studies GLPG0634-CL-205, -223, -224, and GS-US-379-1582), and phase III studies (the FINCH1, FINCH2, FINCH3, and FINCH4 studies)

respect to dissolution behavior between the 100 mg tablet and the 200 mg tablet of the intended commercial formulation.

Concentrations of filgotinib and GS-829845 in human plasma and urine were measured by LC-MS/MS (lower limit of quantitation: in plasma, 1 ng/mL [filgotinib] and 1-2 ng/mL [GS-829845]; in urine, 1 ng/mL [filgotinib and GS-829845]). Unless otherwise specified, dose levels are expressed as filgotinib free-base equivalent; pharmacokinetic parameters and measurements are presented as the mean ± standard deviation. Hereinafter, the formulations in this report are referred to as "FILGOTINIB" for filgotinib [redacted] or "filgotinib maleate" for filgotinib maleate when different formulations are discussed.

6.1.1 Relative bioavailability study (CTD 5.3.1.2.1, Study GLPG0634-CL-107 [July 2013 to August 2013])

A randomized, open-label, 3-treatment, 3-period crossover study was conducted in healthy non-Japanese subjects to investigate the relative bioavailability following administration of a single oral dose of Formulation 2 (200 mg [2 × 100-mg capsules]) or Formulation 3 (200 mg [2 × 100-mg tablets]) to subjects in the fasted state, and food effect[15)] on Formulation 3 (200 mg [2 × 100-mg tablets]). The results are summarized in Table 33.

Table 33. Pharmacokinetic parameters of filgotinib and GS-829845 following single oral administration of FILGOTINIB 200 mg

Formulation (Dosing condition)	Analyte	n	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	Geometric least squares mean ratio [90% CI]		
							C_{max}	AUC_{last}	AUC_{inf}
Formulation 2 (fasted)	Filgotinib	12	1.46 ± 0.60	3.79 ± 1.05	3.85 ± 1.09[a)]	1.0 [0.5, 2.5]			
	GS-829845	12	1.44 ± 0.42	51.5 ± 10.5	52.0 ± 10.7	5.0 [2.0, 24.0]			
							versus Formulation 2 (fasted)		
Formulation 3 (fasted)	Filgotinib	12	1.53 ± 0.59	3.99 ± 0.99	4.10 ± 1.06[b)]	0.6 [0.3, 1.5]	1.04 [0.80, 1.35]	1.06 [0.91, 1.23]	1.16 [0.99, 1.36]
	GS-829845	12	1.44 ± 0.43	51.1 ± 12.0	51.7 ± 12.2	4.0 [4.0, 5.0]	1.00 [0.86, 1.15]	0.99 [0.89, 1.10]	0.99 [0.89, 1.09]
							versus Formulation 3 (fasted)		
Formulation 3 (fed)	Filgotinib	12	0.93 ± 0.24	3.73 ± 0.90	3.82 ± 0.93[a)]	2.5 [0.8, 4.0]	0.66 [0.51, 0.85]	0.94 [0.81, 1.10]	0.89 [0.76, 1.04]
	GS-829845	12	1.55 ± 0.18	57.3 ± 12.4	57.9 ± 12.8	5.0 [4.0, 8.0]	1.13 [0.98, 1.31]	1.12 [1.01, 1.25]	1.12 [1.01, 1.24]

Mean ± standard deviation; t_{max}, median [range]
a) n = 11; b) n = 10

6.1.2 Relative bioavailability study (CTD 5.3.1.2.2, Study GS-US-417-3900 [[redacted] to [redacted]])

This relative bioavailability study consisted of Parts A through D. Part A investigated relative bioavailability following single oral administration of Formulation 3 (100 mg [1 × 100-mg tablet] or 200 mg [2 × 100-mg tablets]) or Formulation 4 (100 mg [1 × 100-mg tablet] or 200 mg [1 × 200-mg tablet]) to healthy non-Japanese subjects in the fasted state using a randomized, open-label, 2-treatment, 2-period crossover design while Part B investigated the food effect[16)] on Formulation 4 (200 mg [1 × 200-mg tablet]) in healthy non-Japanese subjects. The results are summarized in Table 34. In Parts C and D, the effects of antacids[17)] or P-gp inhibitors[18)] on Formulation 4 (100 or 200 mg tablets) were evaluated [see Section 6.2.3].

[15)] The food effect was evaluated using a high-fat meal (approximately 800-1,000 kcal with fat representing approximately 50% of total energy).
[16)] The food effect was evaluated using a high-fat meal (approximately 800 kcal with fat representing approximately 50% of total energy) and a low-fat meal (approximately 400 kcal with fat representing approximately 20% of total energy).
[17)] The effect of antacids was evaluated by prior administration of omeprazole 40 mg once daily (from 5 days prior to study drug treatment) or famotidine 40 mg twice daily (from 4 days prior to study drug treatment).
[18)] The effect of P-gp inhibitors was evaluated by co-administration of itraconazole 200 mg.

Table 34. Pharmacokinetic parameters of filgotinib and GS-829845 following a single oral administration of FILGOTINIB or filgotinib maleate

Part/dose (Dosing condition)		Analyte	n	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	Geometric least squares mean ratio[a)] [90% CI]		
								C_{max}	AUC_{last}	AUC_{inf}
A	Formulation 3 200 mg (fasted)	Filgotinib	26	1.83 ± 0.82	5.45 ± 1.53	5.48 ± 1.51	1.0 [0.5, 4.0]			
		GS-829845	26	2.10 ± 0.37	65.1 ± 12.7	66.7 ± 13.9	4.0 [2.0, 8.0]			
	Formulation 4 200 mg (fasted)	Filgotinib	26	1.78 ± 0.64	5.29 ± 1.46	5.31 ± 1.46	1.0 [0.5, 4.0]	1.01 [0.87, 1.18]	0.98 [0.91, 1.05]	0.97 [0.91, 1.04]
		GS-829845	26	2.15 ± 0.35	64.9 ± 15.1	66.2 ± 16.2	4.0 [3.0, 8.0]	1.03 [0.97, 1.09]	0.99 [0.94, 1.04]	0.99 [0.94, 1.04]
	Formulation 3 100 mg (fasted)	Filgotinib	26	0.85 ± 0.43	2.30 ± 0.67	2.31 ± 0.67	1.0 [0.5, 3.0]			
		GS-829845	26	1.14 ± 0.20	32.5 ± 7.16	32.9 ± 7.46	4.0 [3.0, 8.0]			
	Formulation 4 100 mg (fasted)	Filgotinib	26	0.92 ± 0.33	2.31 ± 0.58	2.33 ± 0.58	1.0 [0.5, 3.1]	1.16 [0.98, 1.36]	1.01 [0.95, 1.08]	1.01 [0.95, 1.08]
		GS-829845	26	1.19 ± 0.22	32.7 ± 6.59	33.2 ± 6.81	4.0 [2.0, 8.0]	1.04 [0.98, 1.11]	1.01 [0.97, 1.06]	1.01 [0.97, 1.06]
B	Formulation 4 200 mg (fasted)	Filgotinib	13	1.88 ± 0.59	5.13 ± 1.16	5.15 ± 1.16	1.0 [0.5, 3.0]			
		GS-829845	13	2.10 ± 0.37	60.9 ± 16.8	62.0 ± 17.8	6.0 [3.0, 8.0]			
	Formulation 4 200 mg (after low-fat meal)	Filgotinib	13	1.65 ± 0.45	5.18 ± 1.35	5.20 ± 1.35	2.0 [1.0, 3.0]	0.89 [0.73, 1.09]	1.01 [0.93, 1.09]	1.01 [0.93, 1.09]
		GS-829845	13	2.12 ± 0.44	67.7 ± 14.2	69.2 ± 14.8	6.0 [4.0, 8.0]	1.00 [0.96, 1.05]	1.13 [1.07, 1.18]	1.13 [1.08, 1.19]
	Formulation 4 200 mg (after high-fat meal)	Filgotinib	13	1.60 ± 0.76	5.03 ± 1.69	5.05 ± 1.69	3.0 [0.5, 4.0]	0.80 [0.66, 0.98]	0.96 [0.88, 1.04]	0.96 [0.88, 1.04]
		GS-829845	13	1.96 ± 0.39	60.0 ± 14.4	61.0 ± 15.0	6.0 [4.0, 8.0]	0.93 [0.89, 0.97]	0.99 [0.95, 1.04]	1.00 [0.95, 1.05]

Mean ± standard deviation; t_{max}, median [range]

a) Part A, geometric mean ratios of the Formulation 4 vs. Formulation 3 (fasted); Part B, geometric mean ratios of the fed vs. fasted states for Formulation 4

6.2 Clinical pharmacology

Clinical pharmacology data including results from the following studies were submitted: studies in healthy subjects, patients with RA, subjects with hepatic or renal impairment, pharmacokinetic drug interaction studies, and population pharmacokinetic analyses. *In vitro* studies with human biomaterials are discussed in Sections 4.1, 4.2, 4.3, and 4.5. Unless otherwise specified, dose levels are expressed as filgotinib free-base equivalent; pharmacokinetic parameters and measurements are presented as the mean ± standard deviation.

6.2.1 Investigation in healthy subjects

6.2.1.1 Phase I study (CTD 5.3.3.3.3, Study GLPG0634-CL-110 [from June 2014 to September 2014])

FILGOTINIB 50, 100, 200 mg or placebo was administered to healthy subjects (26 Japanese and 10 non-Japanese subjects) orally once daily for 10 days. Steady state was reached by Day 2 for filgotinib and Day 3 for GS-829845, with steady-state pharmacokinetic parameters of filgotinib and GS-829845 summarized in Table 35. While filgotinib parameters exhibited dose-proportionality within the range of concentrations studied, there was a more than dose-proportional increase in GS-829845 parameters at 200 mg. Multiple dosing did not result in accumulation of filgotinib; in contrast, GS-829845 tended to accumulate. Following administration of multiple oral doses of FILGOTINIB 200 mg, Japanese to non-Japanese geometric least squares mean ratio and its 90% confidence interval (CI) for filgotinib parameters were 1.01 [0.46, 2.24] (C_{max}) and 0.82 [0.57, 1.17] ($AUC_{0\text{-}24h}$), and those for GS-829845 parameters were 1.10 [0.76, 1.58] (C_{max}) and 1.08 [0.78, 1.50] ($AUC_{0\text{-}24h}$).

Table 35. Pharmacokinetic parameters of filgotinib and GS-829845 in healthy subjects at steady state following multiple oral doses of FILGOTINIB

Analyte	Subject	Dose	Time point	n	C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)	$t_{1/2}$ (h)	t_{max} (h)	CL_R (L/h)
Filgotinib	Japanese	50 mg	Day 1	6	0.33 ± 0.14	0.82 ± 0.30	5.70 ± 1.10	1.0 [0.5, 3.0]	5.54 ± 0.72
			Day 10	6	0.41 ± 0.22	0.89 ± 0.33	6.10 ± 1.39	0.6 [0.5, 1.5]	5.82 ± 0.74
		100 mg	Day 1	6	0.94 ± 0.48	1.99 ± 0.47	4.80 ± 0.79	0.8 [0.3, 1.5]	5.36 ± 1.14
			Day 10	6	0.86 ± 0.31	1.90 ± 0.36	5.17 ± 0.90	1.0 [0.3, 3.0]	6.88 ± 1.64
		200 mg	Day 1	6	4.78 ± 2.48	7.98 ± 1.66	4.77 ± 1.05	1.0 [0.3, 3.0]	3.47 ± 0.91
			Day 10	6	3.77 ± 2.01	6.08 ± 1.69	6.35 ± 2.25	0.5 [0.3, 5.0]	5.04 ± 1.64
	Non-Japanese	200 mg	Day 1	6	2.41 ± 0.99	5.65 ± 1.95	4.48 ± 0.87	0.9 [0.5, 3.0]	3.53 ± 0.82
			Day 10	6	3.06 ± 1.56	5.58 ± 1.19	10.7 ± 7.28	0.4 [0.3, 0.8]	4.93 ± 0.88
GS-829845	Japanese	50 mg	Day 1	6	0.52 ± 0.06	8.45 ± 0.75	—	3.0 [1.5, 5.0]	1.94 ± 0.39
			Day 10	6	0.87 ± 0.13	13.0 ± 2.31	16.4 ± 3.98	2.3 [0.8, 3.0]	2.25 ± 0.28
		100 mg	Day 1	6	1.26 ± 0.27	17.4 ± 2.82	—	3.0 [3.0, 5.0]	1.81 ± 0.35
			Day 10	6	1.87 ± 0.41	29.1 ± 6.34	16.4 ± 3.67	3.0 [2.0, 5.0]	1.89 ± 0.37
		200 mg	Day 1	6	2.90 ± 0.70	48.3 ± 10.4	—	3.0 [3.0, 5.0]	1.10 ± 0.23
			Day 10	6	5.09 ± 0.46	81.4 ± 10.2	16.7 ± 2.44	1.5 [0.8, 12.0]	1.23 ± 0.22
	Non-Japanese	200 mg	Day 1	6	2.22 ± 0.79	34.1 ± 7.19	—	3.0 [1.5, 5.0]	1.38 ± 0.64
			Day 10	6	3.87 ± 1.41	62.1 ± 16.8	19.6 ± 4.64	3.0 [0.5, 3.0]	1.59 ± 0.46

Mean ± standard deviation; t_{max}, median [range]; —, not calculated

6.2.1.2 Mass balance study (CTD 5.3.3.1.3, Study GLPG0634-CL-105 [March 2013 to April 2013])

A single oral dose of ^{14}C-labeled filgotinib 100 mg was administered to healthy non-Japanese subjects (N = 6) in the fed state. Median t_{max} values were 4.0 hours for plasma radioactivity, 1.0 hour for plasma filgotinib, and 5.0 hours for plasma GS-829845. The exposure (AUC_{last}) of filgotinib and GS-829845 accounted for 2.86% and 91.1%, respectively, of the total radioactivity in plasma, with the GS-829845 to filgotinib ratio being 32.2. Up to 216 hours post-dose, 102% of radioactivity was recovered in total, with 86.9% in urine and 15.4% in feces. In urine (up to 168 hours post-dose), 9.37 ± 1.14% of the dose was excreted as filgotinib and 54.0 ± 4.56% of the dose as GS-829845; other metabolites identified were GS-829845-N-glucuronide, M1, M1-O-glucuronide, M3, and 3 types of metabolites with unidentified structures. In feces (up to 168 hours post-dose), 4.47 ± 2.52% of the dose was excreted as filgotinib and 8.88 ± 2.65% as GS-829845; other metabolites identified were GS-829845-N-glucuronide, M1, M3, and 3 types of metabolites with unidentified structures.

6.2.2 Investigation of intrinsic factors

6.2.2.1 Study in patients with hepatic impairment (CTD 5.3.3.3.4, Study GS-US-417-4048 [April 2018 to August 2018])

A single oral dose of filgotinib maleate 100 mg was administered to 10 non-Japanese patients with moderate hepatic impairment (Child-Pugh B) and 10 non-Japanese subjects with normal hepatic function in the fasted state. Table 36 shows the pharmacokinetic parameters of filgotinib and GS-829845. In the normal hepatic function group, 1 subject had significantly low C_{max} and AUC_{inf} values compared with other subjects (≥2 times the standard deviation of the mean of log-transformed values), and therefore, a sensitivity analysis was also performed without this subject. When the subject was excluded, the geometric least squares mean ratio (subjects with moderate hepatic impairment to subjects with normal function) and its 90% CI for filgotinib parameters were 0.83 [0.60, 1.14] (C_{max}) and 1.14 [0.88, 1.47] (AUC_{inf}), and those for GS-829845 parameters were 0.78 [0.64, 0.95] (C_{max}) and 0.92 [0.72, 1.19] (AUC_{inf}).

Table 36. Pharmacokinetic parameters of filgotinib and GS-829845 following a single oral dose of filgotinib maleate 100 mg

Analyte	Severity of hepatic impairment	n	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	Geometric least squares mean ratio [90% CI] (hepatic impairment/normal hepatic function)	
						C_{max}	AUC_{inf}
Filgotinib	Normal	10	0.80 ± 0.49	2.00 ± 1.00	5.29 ± 1.76		
	Moderate	10	0.72 ± 0.29	2.42 ± 0.53	8.08 ± 3.56	1.16 [0.59, 2.29]	1.59 [0.82, 3.08]
GS-829845	Normal	10	1.12 ± 0.45	32.1 ± 14.3	19.3 ± 5.05		
	Moderate	10	0.97 ± 0.26	33.3 ± 11.6	18.9 ± 5.01	1.03 [0.60, 1.76]	1.22 [0.70, 2.14]

Mean ± standard deviation

6.2.2.2 Study in patients with renal impairment (CTD 5.3.3.3.2, Study GLPG0634-CL-106 [March 2014 to July 2014])

FILGOTINIB 100 mg was administered to 15 non-Japanese subjects with renal impairment (6 with mild impairment [eGFR, 60-89 mL/min/1.73 m^2]; 6 with moderate impairment [eGFR, 30-59 mL/min/1.73 m^2]; and 3 with severe impairment [eGFR, 15-29 mL/min/1.73 m^2]) and 9 non-Japanese subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2) orally once daily in the fasted state for 10 days. Table 37 shows the pharmacokinetic parameters of filgotinib and GS-829845 at steady state.

Table 37. Pharmacokinetic parameters of filgotinib and GS-829845 at steady state following multiple oral doses of FILGOTINIB 100 mg

Analyte	Severity of renal impairment	n	C_{max} (μg/mL)	AUC_{0-24h} (μg·h/mL)	$t_{1/2}$ (h)	Geometric least squares mean ratio [90% CI] (renal impairment/normal renal function)	
						C_{max}	AUC_{0-24h}
Filgotinib	Normal	9	0.88 ± 0.51	1.82 ± 0.93[a)]	5.42 ± 1.64[a)]		
	Mild	6	0.78 ± 0.47	1.89 ± 0.55	10.9 ± 5.12	0.82 [0.34, 2.02]	1.11 [0.61, 2.03]
	Moderate	6	0.94 ± 0.45	2.69 ± 1.14[b)]	10.6 ± 7.99	1.01 [0.41, 2.47]	1.42 [0.76, 2.66]
	Severe	3	0.92 ± 0.11	2.64 ± 0.90	9.03 ± 4.63	1.16 [0.37, 3.62]	1.54 [0.72, 3.29]
GS-829845	Normal	9	1.63 ± 0.52	24.9 ± 7.91	20.8 ± 3.56		
	Mild	6	1.54 ± 0.48	30.1 ± 8.83	25.4 ± 6.31	0.94 [0.59, 1.5]	1.21 [0.79, 1.85]
	Moderate	6	2.35 ± 0.83	42.7 ± 16.4	31.7 ± 7.89	1.4 [0.88, 2.25]	1.67 [1.09, 2.56]
	Severe	3	3.43 ± 0.50	66.6 ± 12.3	43.6 ± 5.52	2.17 [1.19, 3.93]	2.74 [1.59, 4.71]

Mean ± standard deviation; a) n = 8; b) n = 5

6.2.2.3 Study in elderly subjects (CTD 5.3.3.3.1, Study GLPG0634-CL-104 [July 2012 to September 2012])

FILGOTINIB 100 mg was administered to 30 healthy elderly subjects (10 subjects in each age group, 40-50 years, 65-74 years, and ≥75 years) orally once daily in the fed state for 10 days. Table 38 shows the pharmacokinetic parameters of filgotinib and GS-829845 at steady state. The GS-829845 to filgotinib exposure ratios were similar across the age groups, ranging from 18.4 to 19.4, suggesting no effect of age on CES involved in formation of major metabolites.

Table 38. Pharmacokinetic parameters of filgotinib and GS-829845 at steady state following multiple oral doses of FILGOTINIB 100 mg

Analyte	Age	n	C_{max} (μg/mL)	AUC_{0-24h} (μg·h/mL)	$t_{1/2}$ (h)	t_{max} (h)	CL_R (L/h)
Filgotinib	40-50	10	0.44 ± 0.14	1.60 ± 0.51	6.07 ± 3.54[a)]	2.0 [1.0, 5.0]	5.55 ± 1.11[b)]
	65-74	10	0.58 ± 0.23	1.79 ± 0.43	5.83 ± 1.36[b)]	2.0 [0.5, 3.0]	3.90 ± 0.91[c)]
	≥75	10	0.63 ± 0.20	2.22 ± 0.46	6.90 ± 2.51[a)]	2.0 [0.5, 3.0]	3.33 ± 0.67[b)]
GS-829845	40-50	10	1.69 ± 0.45	29.4 ± 8.0	17.8 ± 3.2	4.0 [2.0, 5.0]	1.25 ± 0.24[b)]
	65-74	10	1.90 ± 0.30	34.2 ± 5.9	24.7 ± 5.7	3.0 [3.0, 5.0]	1.13 ± 0.24[c)]
	≥75	10	2.20 ± 0.43	40.9 ± 9.0	23.5 ± 5.0	5.0 [3.0, 5.0]	0.93 ± 0.27[b)]

Mean ± standard deviation; t_{max}, median [range]; a) n = 7; b) n = 8; c) n = 9

6.2.3 Pharmacokinetic drug interactions[19)]

Four studies were conducted to investigate drug-drug interactions between filgotinib (filgotinib maleate or FILGOTINIB) and other coadministered drugs. The geometric least squares mean ratio (coadministered versus alone) for the pharmacokinetic parameters of filgotinib or coadministered drugs are shown in Table 39 and Table 40. The results showed that drug-drug interactions are unlikely to occur between filgotinib and any of the drugs studied, and that dose adjustment of filgotinib or the coadministered drugs will not be necessary in clinical settings.

Table 39. Effects of coadministered drugs on pharmacokinetic parameters of filgotinib and GS-829845

Dosage regimen (all drugs were administered orally)		n	Analyte	Geometric least squares mean ratio [90% CI] (coadministered/alone)	
Coadministered drug	Filgotinib maleate			C_{max}	AUC_{inf}
Itraconazole 200 mg, single dose	100 mg, single dose	13	Filgotinib	1.64 [1.29, 2.08]	1.45 [1.33, 1.57]
			GS-829845	0.94 [0.89, 1.01]	1.07 [1.04, 1.10]
Rifampicin 600 mg QD	200 mg, single dose	14	Filgotinib	0.74 [0.64, 0.86]	0.73 [0.69, 0.77]
			GS-829845	0.81 [0.77, 0.85]	0.62 [0.58, 0.66]
Famotidine 40 mg BID	200 mg, single dose	13	Filgotinib	0.82 [0.71, 0.96]	0.98 [0.91, 1.06]
			GS-829845	0.95 [0.88, 1.02]	1.04 [0.96, 1.12]
Omeprazole 40 mg QD	200 mg, single dose	13	Filgotinib	0.73 [0.63, 0.86]	0.89 [0.83, 0.96]
			GS-829845	1.00 [0.95, 1.06]	1.01 [0.98, 1.04]

Table 40. Effects of filgotinib maleate or FILGOTINIB on pharmacokinetic parameters of coadministered drugs

Dosage regimen (all drugs were administered orally)		n	Geometric least squares mean ratio [90% CI] (coadministered/alone)	
Filgotinib maleate or FILGOTINIB	Coadministered drug (single dose)		C_{max}	AUC_{inf}
FILGOTINIB 200 mg QD	Midazolam 2 mg	20	0.99 [0.88, 1.13] 1.09 [0.96, 1.24]	1.05 [0.95, 1.17] 1.11 [0.98, 1.25]
Filgotinib maleate200 mg QD	Ethinyl estradiol 30 μg	24	1.14 [1.06, 1.22]	1.14 [1.09, 1.18]
Filgotinib maleate 200 mg QD	Levonorgestrel 150 μg	24	1.05 [0.95, 1.17]	0.95 [0.90, 1.00]
Filgotinib maleate 200 mg QD	Metformin 850 mg	12	1.02 [0.85, 1.21]	1.02 [0.85, 1.22]

In the midazolam co-administration column, values in the upper row are for midazolam, and values in the lower row are for 1'-OH midazolam.

6.2.4 QT/QTc study (CTD 5.3.4.1.1, Study GS-US-417-3911 [[redacted] to [redacted]])

The study was conducted in healthy non-Japanese subjects (N = 52) using a 4-treatment, 4-period crossover design to evaluate the effect on QT intervals when placebo or filgotinib maleate 200 or 450 mg was administered orally once daily for 7 days using moxifloxacin (400 mg, single dose, orally) as a positive control. The maximum difference in the least squares mean change from baseline in QT interval[20)] between filgotinib maleate 200 mg and placebo with its 90% CI was 2.71 [0.36, 5.07] ms (8 hours post-dose), and the maximum difference between filgotinib maleate 450 mg and placebo was 5.95 [3.54, 8.35] ms (8 hours post-dose). The risk of QT prolongation with filgotinib maleate was determined to be absent as the thorough QT study was negative with the upper limit of the 90% CI being <10 ms. The maximum difference between moxifloxacin and placebo with its 96.67% CI was 12.32 [9.26, 15.38] ms (2 hours post-dose).

[19)] CTD 5.3.1.2.2, Study GS-US-417-3900 [[redacted]]; CTD 5.3.3.4.1, Study GLPG0634-CL-103 [January 2013 to April 2013]; CTD 5.3.3.4.2, Study GS-US-417-3916 [[redacted]]; CTD 5.3.3.4.3, Study GS-US-417-4107 [[redacted]]

[20)] QT intervals calculated by Fridericia's correction formula

6.3 Population pharmacokinetic analysis (CTD 5.3.3.5.1)

A population pharmacokinetic analysis was performed using plasma filgotinib and GS-829845 data (3,176 subjects at 14,060 time points for filgotinib; 3,202 subjects at 16,000 time points for GS-829845) from 14 studies[21] conducted in healthy subjects or patients with RA in and outside Japan (NONMEM version 7.4.3).

The base model for filgotinib was described by a two-compartment model with first-order absorption with a lag time. The following covariates were selected by the covariate search[22]: status in RA (patient with RA vs. healthy subject) and baseline C-reactive protein (CRP) on CL/F; food conditions (always after meals vs. not after meals) on k_a. These covariates were incorporated into the final model.

The base model for GS-829845 was described by a one-compartment model with zero-order absorption and first-order absorption. After covariate search,[23] creatinine clearance (CL_{Cr}) on CL/F and status in RA (patient with RA vs. healthy subject) on V_c/F were selected as significant covariates, which were incorporated into the final model.

Table 41 shows the pharmacokinetic parameters of filgotinib and GS-829845 estimated by the final model following administration of filgotinib maleate 100 or 200 mg orally once daily to Japanese and non-Japanese patients with RA enrolled in phase III studies (the FINCH1, FINCH2, and FINCH3 studies).

Table 41. Pharmacokinetic parameters of filgotinib and GS-829845 estimated by the final model following administration of filgotinib maleate 100 or 200 mg

			AUC_{tau} (μg·h/mL)	C_{max} (μg/mL)	C_{tau} (μg/mL)
200 mg QD, orally	Japanese	Filgotinib	4.45 (25.0)	1.03 (42.4)	0.013 (42.1)
		GS-829845	74.1 (19.1)	3.55 (16.6)	2.51 (25.0)
	Non-Japanese	Filgotinib	4.56 (42.2)	1.05 (60.0)	0.015 (128)
		GS-829845	75.1 (25.2)	3.59 (21.6)	2.58 (33.8)
100 mg QD, orally	Japanese	Filgotinib	2.23 (25.0)	0.51 (42.4)	0.006 (42.1)
		GS-829845	37.0 (19.1)	1.77 (16.6)	1.26 (25.0)
	Non-Japanese	Filgotinib	2.28 (42.2)	0.52 (60.0)	0.007 (128)
		GS-829845	37.6 (25.2)	1.79 (21.6)	1.29 (33.8)

Mean (CV%)

6.R Outline of the review conducted by PMDA

6.R.1 Differences in pharmacokinetics of filgotinib between Japanese and non-Japanese populations

The applicant's explanation about the differences in the pharmacokinetics of filgotinib:

In the phase I study in healthy Japanese and non-Japanese adults [see Section 6.2.1.1], there were no clear differences in the pharmacokinetics of filgotinib between the Japanese and non-Japanese populations. In the population pharmacokinetic analysis [see Section 6.3] based on data from clinical studies in and outside Japan, race was not a significant covariate for any of the pharmacokinetic parameters of filgotinib and GS-829845.

[21] Phase I studies (Studies GS-US-417-3900, -3916, -3911, GLPG0634-CL-101, -102, -104, and -110); phase II studies in patients with RA (Studies GLPG0634-CL-201, -202, -203, and -204); phase III studies (the FINCH1, FINCH2, and FINCH3 studies)

[22] The following covariates were tested for the parameters: age, sex, race, body weight, status in RA, duration of RA, and baseline levels of CL_{cr}, bilirubin, ALT, AST, and CRP (for effects on CL/F and V_c/F); age, sex, race, body weight, status in RA, baseline CRP, duration of RA, and food conditions (for effects on T_{lag}).

[23] Age, sex, race, body weight, status in RA, duration of RA, and baseline levels of CL_{cr}, bilirubin, ALT, AST, and CRP were tested as covariates for the effects on CL/F and V_c/F.

Furthermore, the pharmacokinetic parameters of filgotinib and GS-829845 estimated by the final model for the Japanese population do not differ significantly from those for the non-Japanese population.

The above results indicated that no clinically relevant differences were observed in the pharmacokinetics of filgotinib between Japanese and non-Japanese subjects.

PMDA accepted the applicant's explanation.

6.R.2 Dose adjustment of filgotinib in patients with hepatic or renal impairment

The applicant's explanation about the necessity of dose adjustment of filgotinib in patients with hepatic or renal impairment:

The results of the pharmacology study conducted in patients with hepatic impairment [see Section 6.2.2.1] did not show significant difference in filgotinib or GS-829845 exposure between subjects with normal hepatic function and subjects with moderate hepatic impairment after administration of filgotinib maleate; therefore, dose adjustment for filgotinib maleate will not be necessary in patients with mild or moderate hepatic impairment.

In the pharmacology study conducted in patients with renal impairment [see Section 6.2.2.2], GS-829845 exposures tended to increase depending on the degree of renal impairment. Table 42 shows pharmacokinetic parameters of filgotinib and GS-829845 by severity of renal impairment from the population pharmacokinetic analysis which included results from the phase III studies (the FINCH1, FINCH2, and FINCH3 studies) in which subjects with mild or moderate renal impairment (CL_{cr} ≥40 mL/min) were also enrolled.

The above findings indicated that no dosage adjustment of filgotinib maleate is required in patients with mild or moderate renal impairment since clinically relevant increase in exposure is not expected. However, given that the exposure of GS-829845 increased approximately 2.7-fold in patients with severe renal impairment, it is appropriate to reduce the dose of filgotinib maleate to 100 mg.

Table 42. Pharmacokinetic parameters of filgotinib and GS-829845 by severity of renal impairment following administration of filgotinib maleate 200 mg once daily to patients with RA

Severity of renal impairment CL_{cr}, median [range]	n (%)	Analyte	AUC_{tau} (μg·h/mL)	C_{max} (μg/mL)	Geometric least squares mean ratio [90% CI] (renal impairment/normal renal function)	
					AUC_{tau}	C_{max}
Normal 121.9 [90.0, 311.8]	2,118 (73)	Filgotinib	4.55 (42.9)	1.03 (61.3)		
	2,141 (73)	GS-829845	69.1 (24.2)	3.36 (22.9)		
Mild 78.5 [60.0, 90.0]	677 (23)	Filgotinib	4.70 (37.5)	1.07 (55.6)	1.04 [1.02, 1.07]	1.06 [1.01, 1.11]
	680 (23)	GS-829845	81.1 (22.8)	3.85 (22.4)	1.18 [1.16, 1.20]	1.15 [1.13, 1.17]
Moderate 54.7 [36.6, 59.8]	95 (3)	Filgotinib	4.86 (29.4)	1.16 (45.6)	1.09 [1.02, 1.15]	1.15 [1.03, 1.29]
	98 (3)	GS-829845	91.5 (30.6)	4.29 (27.0)	1.26 [1.20, 1.32]	1.24 [1.19, 1.29]

Mean (CV%)

Severity of renal impairment based on CL_{cr} (normal, CL_{cr} ≥90 mL/min; mild, CL_{cr} ≥60 and <90 mL/min; moderate, CL_{cr} ≥30 and <60 mL/min)

The pharmacokinetics, efficacy, or safety of filgotinib maleate in patients with severe hepatic impairment (Child-Pugh C) or end-stage renal disease (eGFR <15 mL/min/1.73 m^2) have not been evaluated, and it is

difficult to establish an appropriate dosage regimen for this patient population. Therefore, filgotinib maleate will be contraindicated in the above patient population.

PMDA accepted the applicant's explanation above except for the issue regarding patients with moderate renal impairment. The need for dose adjustment for patients with moderate renal impairment will be discussed in Section 7.R.5.2.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from the 4 studies summarized in Table 43.

Table 43. Major clinical studies on efficacy and safety

Phase	Study ID	Geographical location	Study population	No. of subjects	Dosage regimen (administered orally unless otherwise specified)	Main endpoints
III	GS-US-417-0301 (FINCH1)	Global	Patients with RA who have an inadequate response to MTX	(1) 480 (2) 477 (3) 325 (4) 477	In combination with a stable dose of MTX, (1) filgotinib maleate 100 mg QD (2) filgotinib maleate 200 mg QD (3) adalimumab 40 mg Q2W subcutaneously (4) placebo[a)]	Efficacy Safety
	GS-US-417-0302 (FINCH2)	Global	Patients with RA who have an inadequate response to biologics	(1) 153 (2) 148 (3) 148	In combination with a stable dose of cDMARDs, (1) filgotinib maleate 100 mg QD (2) filgotinib maleate 200 mg QD (3) placebo	Efficacy Safety
	GS-US-417-0303 (FINCH3)	Global	Patients with RA who are naïve to MTX	(1) 207 (2) 417 (3) 210 (4) 418	(1) filgotinib maleate 100 mg QD (in combination with MTX) (2) filgotinib maleate 200 mg QD (in combination with MTX) (3) filgotinib maleate 200 mg QD alone (4) placebo (MTX alone)	Efficacy Safety
	GS-US-417-0304 (FINCH4)	Global	Patients with RA who completed FINCH1, FINCH2, or FINCH3	2,729[b)]	Filgotinib maleate 100 mg or 200 mg QD	Efficacy Safety

a) During and after Week 24, filgotinib maleate 100 mg or 200 mg was administered orally once daily
b) Data cut-off on September 16, 2019

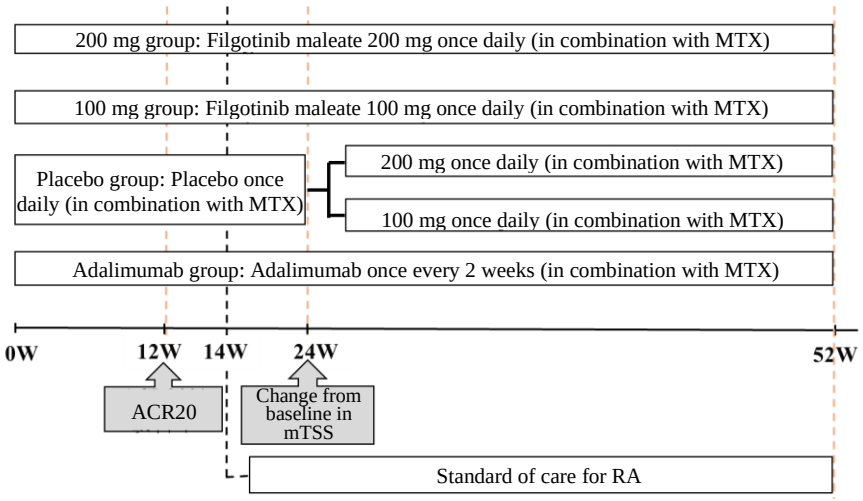
7.1 Phase III studies

7.1.1 Global study in patients with RA who had an inadequate response to MTX (CTD 5.3.5.1.6 and 5.3.5.1.10, Study GS-US-417-0301 [the FINCH1 study] [August 2016 to June 2019])

A randomized, double-blind, parallel-group, placebo-controlled study was conducted to investigate the efficacy and safety of filgotinib in patients with RA[24)] who had an inadequate response to MTX (target sample size, 1,650 subjects; 450 [100 mg], 450 [200 mg], 300 [adalimumab], and 450 [placebo]) in 30 countries and regions including Japan, Poland, Ukraine, and the US.

[24)] Key inclusion criteria: patients with RA aged ≥18 years (≥20 years in Japan) who meet all of the following: (1) have a diagnosis of RA according to 2010 American College of Rheumatology (ACR)/the European League Against Rheumatism (EULAR) criteria for RA, with ACR functional class I, II, or III; (2) both swollen joint count (SJC) and tender joint count (TJC) ≥6 at screening and baseline; (3) one of the following conditions in A through C is applicable at screening: A, ≥1 documented joint erosion on radiographs of the hands, wrists or feet, and positivity for either anti-cyclic citrullinated peptide (CCP) antibodies or rheumatoid factor (RF); B, ≥3 documented joint erosion on radiographs of the hands, wrists or feet; C, CRP ≥6 mg/L; (4) use of MTX for ≥12 weeks and a stable dose of 7.5 to 25 mg/week for ≥4 weeks (stable dose of <7.5 mg/week were allowed if intolerant to higher doses or other specific cases); (5) no prior treatment with JAK inhibitors or adalimumab and no prior treatment failure with biologics (acceptable if treatment failure with only 1 biologic drug and the exposure is limited to <3 months).

Subjects received filgotinib maleate 100 mg, 200 mg, or placebo orally once daily in combination with a stable dose of MTX,[25] or adalimumab 40 mg subcutaneously once every 2 weeks in combination with a stable dose of MTX. Subjects who had not achieved at least a 20% improvement from baseline in swollen joint count (SJC) and tender joint count (TJC) at Week 14 were discontinued from study drug treatment and received standard of care for RA as determined by the investigator. The subjects assigned to placebo were randomly reassigned to either filgotinib maleate 100 mg or 200 mg at Week 24 and received the filgotinib maleate 100 mg or 200 mg orally once daily thereafter (Figure 2).



Subjects who had an inadequate response at Week 14 were discontinued from study drug treatment and received standard of care for RA as determined by the investigator.

Figure 2. Study design of the FINCH1 study

Of all randomized subjects (1,759 subjects; 480 [100 mg], 477 [200 mg], 325 [adalimumab], and 477 [placebo]), those who received at least 1 dose of the study drug (1,755 subjects; 480 [100 mg], 475 [200 mg], 325 [adalimumab], and 475 [placebo]) were included in the full analysis set (FAS) and safety analysis set. These subjects in the FAS constituted the efficacy analysis set.

The incidence of study drug discontinuation up to Week 12 was 2.3% (11 of 480) of subjects in the 100 mg group, 2.5% (12 of 475) of subjects in the 200 mg group, 3.4% (11 of 325) of subjects in the adalimumab group, and 6.3% (30 of 475) of subjects in the placebo group. Major reasons for discontinuation included “subject’s decision” (1.0% [5 of 480] of subjects in the 100 mg, 0.4% [2 of 475] of subjects in the 200 mg group, 1.8% [6 of 325] of subjects in the adalimumab group, and 2.3% [11 of 475] of subjects in the placebo group) and “adverse events” (0.6% [3 of 480] of subjects in the 100 mg group, 1.9% [9 of 475] of subjects in the 200 mg group, 0.6% [2 of 325] of subjects in the adalimumab group, and 1.7% [8 of 475] of subjects in the placebo group).

In the Japanese subpopulation of the FAS (147 subjects; 41 [100 mg], 40 [200 mg], 28 [adalimumab], and 38 [placebo]), the incidence of study drug discontinuation up to Week 12 was 2.4% (1 of 41) of subjects in the

[25] Subjects were to take the same dose level of MTX as that defined in the key inclusion criteria (4).

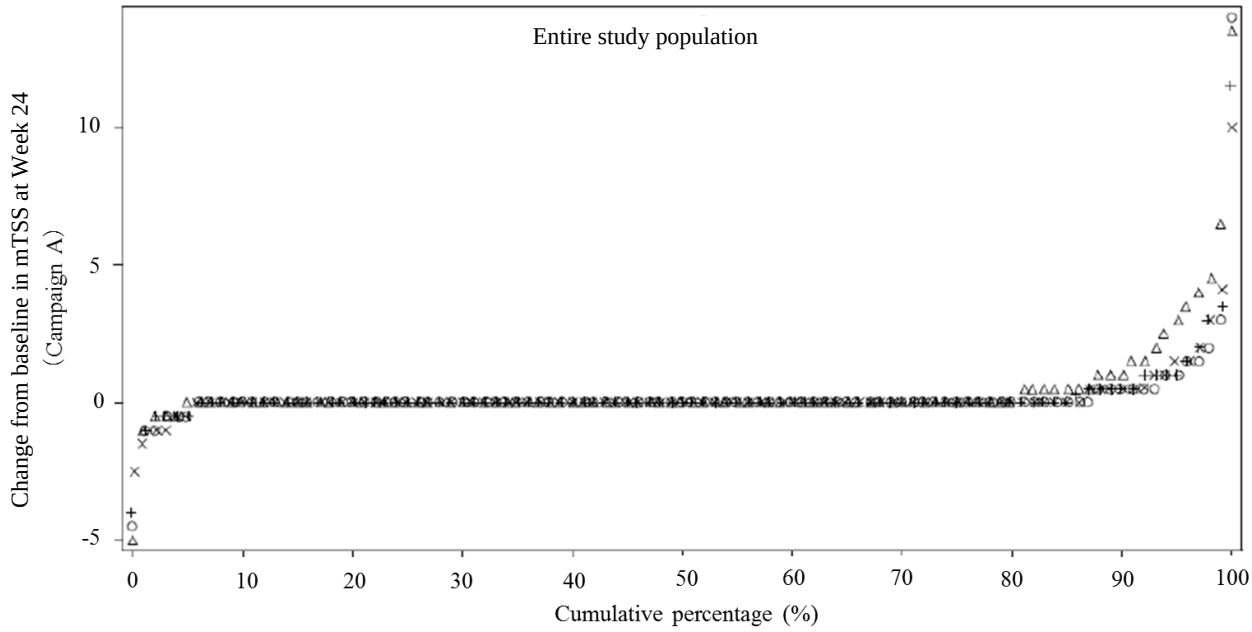
100 mg group, 2.5% (1 of 40) of subjects in the 200 mg group, 3.6% (1 of 28) of subjects in the adalimumab group, and 10.5% (4 of 38) of subjects in the placebo group. Major reasons for discontinuation included "adverse events" (0 subjects in the 100 mg and 200 mg groups, 3.6% [1 of 28] of subjects in the adalimumab group, and 7.9% [3 of 38] of subjects in the placebo group).

The primary efficacy endpoint of the proportion of subjects who achieve an ACR20% improvement response (ACR20) at Week 12 and the change from baseline in van der Heijde modified Total Sharp Score (mTSS) at Week 24 are summarized in Table 44 and plotted in Figure 3. For both endpoints, the results in the 100 mg and 200 mg groups showed a statistically significant difference from placebo, demonstrating the superiority of filgotinib maleate 100 mg and 200 mg over placebo. Table 44 and Figure 4 show the results for the Japanese subpopulation.

Table 44. Results for the primary efficacy endpoint (FAS)

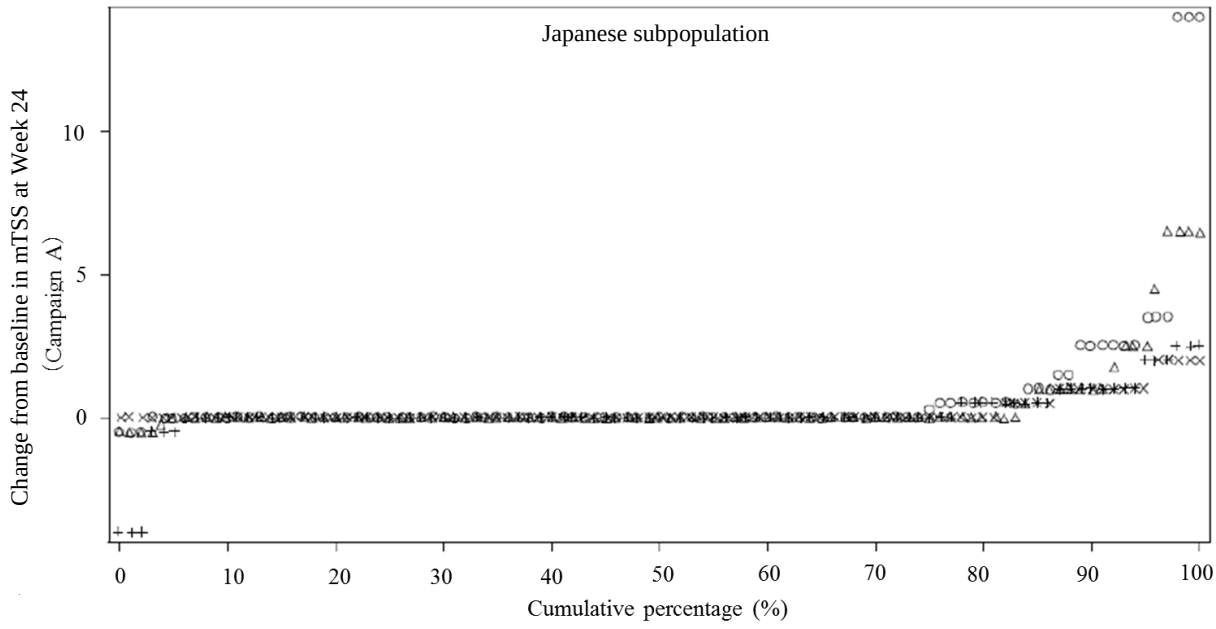
		100 mg	200 mg	Adalimumab	Placebo
Entire study population	ACR20 at Week 12	69.8 (335/480)	76.6 (364/475)	70.5 (229/325)	49.9 (237/475)
	Difference from placebo [95% CI] *P*-value[a), c)]	19.9 [13.6, 26.2] <0.001	26.7 [20.6, 32.8] <0.001		
	Change from baseline in mTSS at Week 24	0.17 ± 0.91 (404)	0.13 ± 0.94 (405)	0.16 ± 0.95 (271)	0.37 ± 1.42 (351)
	Difference from placebo [95% CI][b)] *P*-value[b), c)]	−0.25 [−0.40, −0.10] 0.001	−0.27 [−0.43, −0.12] <0.001		
Japanese sub-population	ACR20 at Week 12	65.9 (27/41)	77.5 (31/40)	53.6 (15/28)	36.8 (14/38)
	Difference from placebo [95% CI]	29.0 [5.4, 52.7]	40.7 [18.0, 63.3]		
	Change from baseline in mTSS at Week 24	0.13 ± 0.92 (36)	0.72 ± 2.43 (36)	0.20 ± 0.50 (22)	0.42 ± 1.39 (25)
	Difference from placebo [95% CI][b)]	−0.42 [−1.23, 0.39]	0.20 [−0.61, 1.01]		

ACR20 response, % (n/N); change from baseline in mTSS, mean ± standard deviation (number of subjects evaluated)
For ACR20, missing data were imputed by nonresponder imputation (NRI).
a) A logistic regression model using treatment, geographical region, prior use of biologics, and result (positive vs. negative) for anti-CCP antibodies or RF at screening as covariates
b) A mixed-effects model for repeated measures (MMRM) using treatment, visit, treatment by visit interaction, geographical region, prior use of biologics, result (positive vs. negative) for anti-CCP antibodies or RF at screening, and baseline values as covariates, assuming an unstructured covariance structure between timepoints (for the Japanese subpopulation analysis, geographical region, prior use of biologics, and result [positive vs. negative] for anti-CCP antibodies or RF at screening were not included in the modeling)
c) Using a two-sided significance level of 5%, the multiplicity of hypothesis tests was adjusted according to the closed testing procedure in the order of 200 mg versus placebo and then 100 mg versus placebo for ACR20, and 200 mg versus placebo and then 100 mg versus placebo for change from baseline in mTSS.



○, 200 mg group; +, 100 mg group; ×, adalimumab group; Δ, placebo group

Figure 3. Cumulative probability distribution plot for change from baseline in mTSS at Week 24 (entire study population)



○, 200 mg group; +, 100 mg group; ×, adalimumab group; Δ, placebo group

Figure 4. Cumulative probability distribution plot for change from baseline in mTSS at Week 24 (Japanese subpopulation)

The incidence of adverse events up to Week 24 was 59.8% (287 of 480) of subjects in the 100 mg group, 60.4% (287 of 475) of subjects in the 200 mg group, 57.2% (186 of 325) of subjects in the adalimumab group, and 53.1% (252 of 475) of subjects in the placebo group. Table 45 shows major adverse events.

Death occurred in 1 of 480 subjects (0.2%) in the 100 mg group (myocardial infarction), 2 of 475 subjects (0.4%) in the 200 mg group (septic shock/pneumonia in 2 subjects), and 2 of 475 subjects (0.4%) in the placebo group (toxicity to various agents, immunodeficiency/bronchopulmonary aspergillosis/septic shock/metabolic

acidosis/acute respiratory failure[26]). A causal relationship to the study drug could not be ruled out for the following events: septic shock/pneumonia, pneumonia in the 200 mg group; immunodeficiency/bronchopulmonary aspergillosis/septic shock/metabolic acidosis/acute respiratory failure in the placebo group.

The incidence of serious adverse events was 5.0% (24 of 480) of subjects in the 100 mg group, 4.4% (21 of 475) of subjects in the 200 mg group, 4.3% (14 of 325) of subjects in the adalimumab group, and 4.2% (20 of 475) of subjects in the placebo group. Among these events, a causal relationship to the study drug could not be ruled out for the following events: erysipelas, cellulitis, cholecystitis, pneumonia, gastritis, skin ulcer/infected skin ulcer, mouth ulceration/stomatitis/candida infection in the 100 mg group; pneumonia, pneumonia/pneumonia, septic shock/pneumonia, paronychia, lipase increased, ALT increased, bronchitis, femoral neck fracture, gastroenteritis in the 200 mg group; pneumonia in 2 subjects, arthritis infective, pustular psoriasis, sinus tachycardia, infective tenosynovitis, AST increased/ALT increased, pneumocystis jirovecii pneumonia, cellulitis in the adalimumab group; pancytopenia/infectious pleural effusion/pneumonia fungal, breast cancer stage I, pneumonia, organising pneumonia, pneumonia pneumococcal in the placebo group.

The incidence of adverse events leading to study drug discontinuation was 1.9% (9 of 480) of subjects in the 100 mg group, 3.2% (15 of 475) of subjects in the 200 mg group, 4.0% (13 of 325) of subjects in the adalimumab group, and 3.2% (15 of 475) of subjects in the placebo group.

The incidence of adverse reactions was 21.7% (104 of 480) of subjects in the 100 mg group, 21.7% (103 of 475) of subjects in the 200 mg group, 21.5% (70 of 325) of subjects in the adalimumab group, and 18.3% (87 of 475) of subjects in the placebo group.

Table 45. Adverse events occurring in ≥3% of subjects in any group (up to Week 24, safety analysis set)

Adverse event	100 mg (N = 480)	200 mg (N = 475)	Adalimumab (N = 325)	Placebo (N = 475)
Nasopharyngitis	29 (6.0)	31 (6.5)	15 (4.6)	25 (5.3)
Upper respiratory tract infection	33 (6.9)	25 (5.3)	17 (5.2)	14 (2.9)
Nausea	10 (2.1)	19 (4.0)	4 (1.2)	7 (1.5)
Hypertension	7 (1.5)	16 (3.4)	9 (2.8)	5 (1.1)
ALT increased	15 (3.1)	13 (2.7)	14 (4.3)	11 (2.3)
Headache	12 (2.5)	10 (2.1)	10 (3.1)	17 (3.6)
Anaemia	15 (3.1)	9 (1.9)	6 (1.8)	11 (2.3)
AST increased	14 (2.9)	9 (1.9)	11 (3.4)	9 (1.9)
Rheumatoid arthritis	6 (1.3)	3 (0.6)	5 (1.5)	19 (4.0)

n (%)

The incidence of adverse events in the Japanese subpopulation up to Week 24 was 73.2% (30 of 41) of subjects in the 100 mg group, 82.5% (33 of 40) of subjects in the 200 mg group, 71.4 % (20 of 28) of subjects in the adalimumab group, and 73.7% (28 of 38) of subjects in the placebo group. Table 46 shows major adverse events.

No deaths occurred.

[26] The event, which occurred ≥30 days after administration of the last dose of the study drug, was not classified as a treatment-emergent adverse event.

Serious adverse events occurred in 2 of 41 subjects (4.9%) in the 100 mg group (nephrolithiasis and renal cell dysplasia), 3 of 40 subjects (7.5%) in the 200 mg group (gastroenteritis, macular fibrosis/vitreous opacities, and coronary artery restenosis), 3 of 28 subjects (10.7%) in the adalimumab group (pneumonia, pneumocystis jirovecii pneumonia, and cellulitis), and 3 of 38 subjects (7.9%) in the placebo group (pneumonia, organising pneumonia, and pneumonia pneumococcal). Among the serious adverse events, a causal relationship to the study drug could not be ruled out for the following events: gastroenteritis in the 200 mg group; pneumonia, pneumocystis jirovecii pneumonia, cellulitis in the adalimumab group; pneumonia, organising pneumonia, pneumonia pneumococcal in the placebo group.

The incidence of adverse events leading to study drug discontinuation was 2.5% (1 of 40) of subjects in the 200 mg group, 7.1% (2 of 28) of subjects in the adalimumab group, and 10.5% (4 of 38) of subjects in the placebo group.

The incidence of adverse reactions was 31.7% (13 of 41) of subjects in the 100 mg group, 37.5% (15 of 40) of subjects in the 200 mg group, 32.1% (9 of 28) of subjects in the adalimumab group, and 31.6% (12 of 38) of subjects in the placebo group.

Table 46. Adverse events occurring in ≥3 subjects in any group (up to Week 24, safety analysis set, Japanese subpopulation)

Adverse event	100 mg (N = 41)	200 mg (N = 40)	Adalimumab (N = 28)	Placebo (N = 38)
Nasopharyngitis	3 (7.3)	7 (17.5)	3 (10.7)	4 (10.5)
Nausea	3 (7.3)	4 (10.0)	0	0
Bronchitis	1 (2.4)	4 (10.0)	0	1 (2.6)
Stomatitis	4 (9.8)	3 (7.5)	0	3 (7.9)
Influenza	2 (4.9)	3 (7.5)	0	1 (2.6)
Dizziness	2 (4.9)	3 (7.5)	0	0
Pharyngitis	0	3 (7.5)	0	3 (7.9)
Blood CPK increased	0	3 (7.5)	0	0
Headache	2 (4.9)	2 (5.0)	1 (3.6)	3 (7.9)
Eczema	1 (2.4)	1 (2.5)	1 (3.6)	3 (7.9)
Rash	3 (7.3)	0	0	0
Rheumatoid arthritis	1 (2.4)	0	1 (3.6)	3 (7.9)

n (%)

From Week 24 to Week 52, adverse events occurred in 224 of 480 subjects (46.7%) in the 100 mg group, 222 of 475 subjects (46.7%) in the 200 mg group, 149 of 325 subjects (45.8%) in the adalimumab group, 97 of 191 subjects (50.8%) in the placebo group who were switched to 100 mg (placebo-100 mg group), and 92 of 190 subjects (48.4%) in the placebo group who were switched to 200 mg (placebo-200 mg group). Table 47 shows major adverse events.

Death occurred in 1 subject in the 200 mg group (bronchitis/alveolitis/bronchiectasis/pulmonary fibrosis/respiratory failure/rheumatoid lung/cor pulmonale chronic), 1 subject in the adalimumab group (sepsis), 1 subject in the placebo-100 mg group (varicella), and 1 subject in the placebo-200 mg group (ischaemic stroke [2 events]/deep vein thrombosis/pulmonary embolism). Among these events, a causal relationship to the study drug could not be ruled out for sepsis in the adalimumab group, varicella in the placebo-100 mg group, and deep vein thrombosis/pulmonary embolism in the placebo-200 mg group.

The incidence of serious adverse events was 3.5% (17 of 480) of subjects in the 100 mg group, 2.9% (14 of 475) of subjects in the 200 mg group, 2.5% (8 of 325) of subjects in the adalimumab group, 4.2% (8 of 191) of subjects in the placebo-100 mg group, and 3.7% (7 of 190) of subjects in the placebo-200 mg group. Among the serious adverse events, a causal relationship to the study drug could not be ruled out for the following events: pneumonia in 2 subjects, pneumonia bacterial, pyelonephritis acute, transient ischaemic attack in the 100 mg group; duodenal ulcer perforation, skin ulcer, pneumonia, arthritis infective, peptic ulcer/vomiting/cholelithiasis, cellulitis/cellulitis, metastases to liver/pancreatic carcinoma, pneumonia viral in the 200 mg group; sepsis in the adalimumab group; varicella, prostatitis in the placebo-100 mg group; and deep vein thrombosis/pulmonary embolism in the placebo-200 mg group.

The incidence of adverse events leading to study drug discontinuation was 1.3% (6 of 480) of subjects in the 100 mg group, 2.3% (11 of 475) of subjects in the 200 mg group, 1.5% (5 of 325) of subjects in the adalimumab group, 1.0% (2 of 191) of subjects in the placebo-100 mg group, and 3.2% (6 of 190) of subjects in the placebo-200 mg group.

The incidence of adverse reactions was 13.3% (64 of 480) of subjects in the 100 mg group, 15.6% (74 of 475) of subjects in the 200 mg group, 11.4% (37 of 325) of subjects in the adalimumab group, 15.2% (29 of 191) of subjects in the placebo-100 mg group, and 11.1% (21 of 190) of subjects in the placebo-200 mg group.

Table 47. Adverse events occurring in ≥3% of subjects in any group (Weeks 24-52, safety analysis set)

Adverse event	100 mg (N = 480)	200 mg (N = 475)	Adalimumab (N = 325)	Placebo-100 mg (N = 191)	Placebo-200 mg (N = 190)
Upper respiratory tract infection	22 (4.6)	18 (3.8)	6 (1.8)	6 (3.1)	8 (4.2)
Nasopharyngitis	24 (5.0)	17 (3.6)	9 (2.8)	6 (3.1)	7 (3.7)
Urinary tract infection	12 (2.5)	10 (2.1)	9 (2.8)	8 (4.2)	10 (5.3)
ALT increased	15 (3.1)	7 (1.5)	11 (3.4)	3 (1.6)	7 (3.7)
AST increased	10 (2.1)	5 (1.1)	9 (2.8)	3 (1.6)	8 (4.2)

n (%)

In the Japanese subpopulation, the incidence of adverse events from Week 24 to Week 52 was 61.0% (25 of 41) of subjects in the 100 mg group, 67.5% (27 of 40) of subjects in the 200 mg group, 53.6% (15 of 28) of subjects in the adalimumab group, 61.5% (8 of 13) of subjects in the placebo-100 mg group, and 75.0% (9 of 12) of subjects in the placebo-200 mg group. Table 48 shows major adverse events.

No deaths occurred.

Serious adverse events occurred in 1 of 41subjects (2.4%) in the 100 mg group (pneumonia bacterial) and in 1 of 40 subjects (2.5%) in the 200 mg group (duodenal ulcer perforation). A causal relationship to the study drug could not be ruled out for both events.

The incidence of adverse events leading to study drug discontinuation was 2.5% (1 of 40) of subjects in the 200 mg group, 3.6% (1 of 28) of subjects in the adalimumab group, and 7.7% (1 of 13) subjects in the placebo-100 mg group.

The incidence of adverse reactions was 34.1% (14 of 41) of subjects in the 100 mg group, 25.0% (10 of 40) of subjects in the 200 mg group, 17.9% (5 of 28) of subjects in the adalimumab group, 30.8% (4 of 13) of subjects in the placebo-100 mg group, and 41.7% (5 of 12) of subjects in the placebo-200 mg group.

Table 48. Adverse events occurring in ≥3 subjects in any group (Weeks 24-52, safety analysis set, Japanese subpopulation)

Adverse event	100 mg (N = 41)	200 mg (N = 40)	Adalimumab (N = 28)	Placebo-100 mg (N = 13)	Placebo-200 mg (N = 12)
Nasopharyngitis	5 (12.2)	8 (20.0)	0	0	1 (8.3)
Influenza	1 (2.4)	4 (10.0)	3 (10.7)	1 (7.7)	1. (8.3)
Contusion	0	3 (7.5)	0	1 (7.7)	0
Fall	0	3 (7.5)	1 (3.6)	0	0
Rheumatoid arthritis	0	1 (2.5)	3 (10.7)	0	0

n (%)

7.1.2 Global study in patients with RA who had an inadequate response to biologics (CTD 5.3.5.1.7, Study GS-US-417-0302 [the FINCH2 study] [July 2016 to March 2018])

A randomized, double-blind, parallel-group, placebo-controlled study was conducted to assess the efficacy and safety of filgotinib in patients with RA who had an inadequate response to or were intolerant to biologics[27)] (target sample size, 423 subjects; n = 141/group) in 15 countries and regions including Japan, the US, and Mexico.

Subjects received filgotinib maleate 100 mg, 200 mg, or placebo orally once daily in combination with a stable dose of cDMARDs,[28)]. Subjects who had failed to achieve at least a 20% improvement from baseline in SJC and TJC at Week 14 were discontinued from study drug treatment and received standard of care for RA as determined by the investigator (Figure 5).

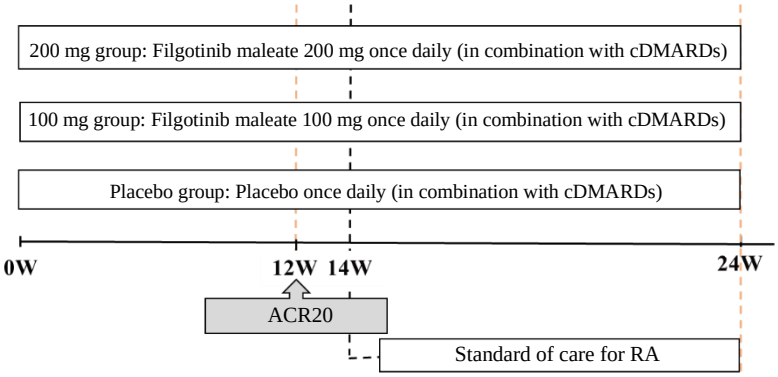


Figure 5. Study design of the FINCH2 study

[27)] Key inclusion criteria: patients with RA aged ≥18 years (≥20 years in Japan) who meet all of the following: (1) have a diagnosis of RA according to 2010 ACR/EULAR criteria for RA, with ACR functional class I, II, or III; (2) both SJC and TJC ≥6 at screening and baseline; (3) CRP ≥ 4 mg/L at screening; (4) ongoing treatment with a stable prescription of 1 or 2 cDMARDs; (5) have received ≥1 biologic for ≥ 12 weeks for the treatment of RA to which they have had an inadequate response or intolerance.

[28)] Subjects were to take the same dose level of cDMARDs as that defined in the key inclusion criteria (4).

Of all randomized subjects (449 subjects; 153 [100 mg], 148 [200 mg], and 148 [placebo]), those who received at least 1 dose of the study drug (448 subjects; 153 [100 mg], 147 [200 mg], and 148 [placebo]) were included in the FAS and safety analysis set. These subjects in the FAS constituted the efficacy analysis set.

The incidence of study drug discontinuation up to Week 12 was 5.2% (8 of 153) of subjects in the 100 mg group, 2.0% (3 of 147) of subjects in the 200 mg group, and 10.1% (15 of 148) of subjects in the placebo group. Major reasons for discontinuation included "adverse events" (2.0% [3 of 153] of subjects in the 100 mg group, 2.0% [3 of 147] of subjects in the 200 mg group, and 2.0% [3 of 148] of subjects in the placebo group) and "subject's decision" (2.0% [3 of 153] of subjects in the 100 mg group, 0 subjects in the 200 mg group, and 4.1% [6 of 148] of subjects in the placebo group).

In the Japanese subpopulation of the FAS (40 subjects; 15 [100 mg], 12 [200 mg], and 13 [placebo]), up to Week 12, study drug discontinuation occurred only in 1 subject in the placebo group due to "protocol deviation."

Table 49 shows the primary efficacy endpoint of the proportion of subjects who achieve an ACR20 response at Week 12. The difference for each of the 100 mg and 200 mg groups versus placebo for the ACR20 was statistically significant, demonstrating the superiority of filgotinib maleate 100 mg and 200 mg over placebo. Results for the Japanese subpopulation were also shown in Table 49.

Table 49. Results for the primary efficacy endpoint (FAS, NRI)

		100 mg	200 mg	Placebo
Entire study population	ACR20 at Week 12	57.5 (88/153)	66.0 (97/147)	31.1 (46/148)
	Difference from placebo [95% CI] *P*-value[a)]	26.4 [15.0, 37.9] <0.001	34.9 [23.5, 46.3] <0.001	—
Japanese subpopulation	ACR20 at Week 12	53.3 (8/15)	83.3 (10/12)	30.8 (4/13)
	Difference from placebo [95% CI]	22.6 [−20.2, 65.3]	52.6 [11.8, 93.3]	—

% (n/N)

a) At a two-sided significance level of 5%, a logistic regression model using treatment, geographical region, number of prior biologics (<3 vs. ≥3), and result (positive vs. negative) for anti-CCP antibodies or RF at screening as covariates.

The incidence of adverse events was 63.4% (97 of 153) of subjects in the 100 mg group, 69.4% (102 of 147) of subjects in the 200 mg group, and 67.6% (100 of 148) of subjects in the placebo group. Table 50 shows major adverse events.

No deaths occurred.

The incidence of serious adverse events was 5.2% (8 of 153) of subjects in the 100 mg group, 4.1% (6 of 147) of subjects in the 200 mg group, and 3.4% (5 of 148) of subjects in the placebo group. Among these serious adverse events, a causal relationship to the study drug could not be ruled out for bronchitis in the 100 mg group and bursitis in the 200 mg group.

The incidence of adverse events leading to study drug discontinuation was 3.9% (6 of 153) of subjects in the 100 mg group, 3.4% (5 of 147) of subjects in the 200 mg group, and 2.0% (3 of 148) of subjects in the placebo group.

The incidence of adverse reactions was 19.0% (29 of 153) of subjects in the 100 mg group, 21.8% (32 of 147) of subjects in the 200 mg group, and 15.5% (23 of 148) of subjects in the placebo group.

Table 50. Adverse events occurring in ≥3% of subjects in any group (safety analysis set)

Adverse event	100 mg (N = 153)	200 mg (N = 147)	Placebo (N = 148)	Adverse event	100 mg (N = 153)	200 mg (N = 147)	Placebo (N = 148)
Nasopharyngitis	9 (5.9)	15 (10.2)	7 (4.7)	Arthralgia	2 (1.3)	5 (3.4)	3 (2.0)
Upper respiratory tract infection	9 (5.9)	8 (5.4)	6 (4.1)	Constipation	2 (1.3)	5 (3.4)	0
Headache	9 (5.9)	8 (5.4)	2 (1.4)	Urinary tract infection	6 (3.9)	4 (2.7)	2 (1.4)
Bronchitis	3 (2.0)	8 (5.4)	8 (5.4)	Pharyngitis	6 (3.9)	2 (1.4)	0
Nausea	8 (5.2)	7 (4.8)	6 (4.1)	Rheumatoid arthritis	2 (1.3)	2 (1.4)	9 (6.1)
Hypertension	5 (3.3)	6 (4.1)	2 (1.4)	Back pain	2 (1.3)	2 (1.4)	5 (3.4)
Influenza	6 (3.9)	5 (3.4)	3 (2.0)	Rash	2 (1.3)	0	5 (3.4)
Diarrhoea	4 (2.6)	5 (3.4)	3 (2.0)				

n (%)

The incidence of adverse events in the Japanese subpopulation was 60.0% (9 of 15) of subjects in the 100 mg group, 75.0% (9 of 12) of subjects in the 200 mg group, and 76.9% (10 of 13) of subjects in the placebo group. Table 51 shows major adverse events.

There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

The incidence of adverse reactions was 33.3% (5 of 15) of subjects in the 100 mg group, 50.0% (6 of 12) of subjects in the 200 mg group, and 30.8% (4 of 13) of subjects in the placebo group.

Table 51. Adverse events occurring in ≥2 subjects in any group (safety analysis set, Japanese subpopulation)

Adverse event	100 mg (N = 15)	200 mg (N = 12)	Placebo (N = 13)
Nasopharyngitis	2 (13.3)	4 (33.3)	2 (15.4)
Influenza	2 (13.3)	1 (8.3)	0
Seasonal allergy	2 (13.3)	1 (8.3)	0
Rheumatoid arthritis	1 (6.7)	0	3 (23.1)

n (%)

7.1.3 Global study in patients with RA who are naïve to MTX (CTD 5.3.5.1.8 and 5.3.5.1.11, Study GS-US-417-0303 [the FINCH3 study] [August 2016 to May 2019])

A randomized, double-blind, parallel-group, placebo- and active-controlled study was conducted to assess the efficacy and safety of filgotinib in patients with RA[29] who are naïve to MTX (target sample size, 1,200 subjects; 200 [100 mg + MTX], 400 [200 mg + MTX], 200 [200 mg alone], and 400 [MTX]) in 31 countries and regions including Japan, the US, Mexico, and India.

Subjects received filgotinib maleate 100 mg, 200 mg, or placebo orally once daily in combination with a stable dose of MTX,[30] or filgotinib maleate 200 mg alone orally once daily. Subjects who had failed to achieve at least a 20% improvement from baseline in SJC and TJC at Week 24 were discontinued from study drug treatment and received standard of care for RA as determined by the investigator (Figure 6).

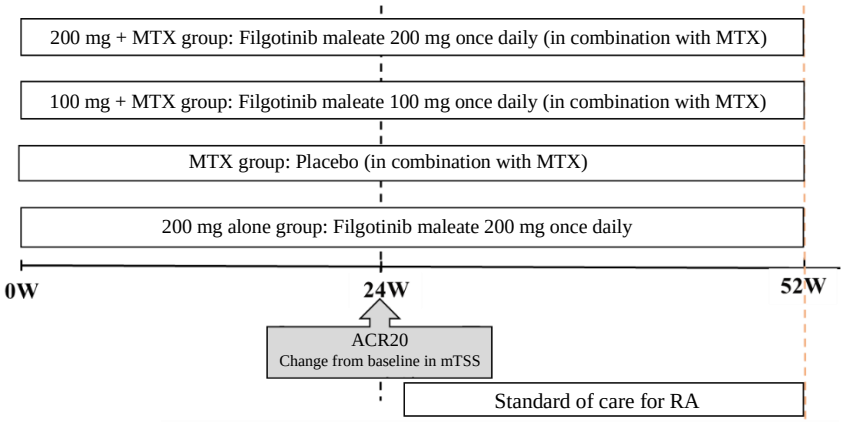


Figure 6. Study design of the FINCH3 study

Of all randomized subjects (1,252 subjects; 207 [100 mg + MTX], 417 [200 mg + MTX], 210 [200 mg alone], and 418 [MTX]), those who received at least 1 dose of the study drug (1,249 subjects; 207 [100 mg + MTX], 416 [200 mg + MTX], 210 [200 mg alone], and 416 [MTX]) were included in the FAS and safety analysis set. These subjects in the FAS constituted the efficacy analysis set.

The incidence of study drug discontinuation up to Week 24 was 6.8% (14 of 207) of subjects in the 100 mg + MTX group, 9.6% (40 of 416) of subjects in the 200 mg + MTX group, 10.5% (22 of 210) of subjects in the 200 mg alone group, and 10.3% (43 of 416) of subjects in the MTX group. Major reasons for discontinuation included “subject’s decision” (3.4% [7 of 207] of subjects in the 100 mg + MTX group, 3.4% [14 of 416] of subjects in the 200 mg + MTX group, 2.9% [6 of 210] of subjects in the 200 mg alone group, and 4.8% [20 of 416] of subjects in the MTX group) and “adverse events” (2.4% [5 of 207] of subjects in the 100 mg + MTX

[29] Key inclusion criteria: patients with RA aged ≥18 years (≥20 years in Japan) who meet all of the following: (1) have a diagnosis of RA according to 2010 ACR/EULAR criteria for RA, with ACR functional class I, II, or III; (2) both SJC and TJC ≥6 at screening and baseline; (3) one of the following conditions in A through C is applicable at screening: A, ≥1 documented joint erosion on radiographs of the hands, wrists or feet; B, positivity for either anti-CCP antibodies or RF; C, CRP ≥4 mg/L; (4) Limited or no prior treatment with MTX for the treatment of RA (no more than 3 doses of MTX ≤25 mg each), and MTX treatment was considered appropriate by the investigator.

[30] The titration period for MTX was the first 8 weeks. Subjects were to be started on 10 mg/week of MTX, and the dose was advanced to 20 mg/week if tolerated. In Japan, subjects were to be started on 7.5 mg/week, and the dose was advanced to 15 mg/week.

group, 4.1% [17 of 416] of subjects in the 200 mg + MTX group, 1.9% [4 of 210] of subjects in the 200 mg alone group, and 1.2% [5 of 416] of subjects in the MTX group).

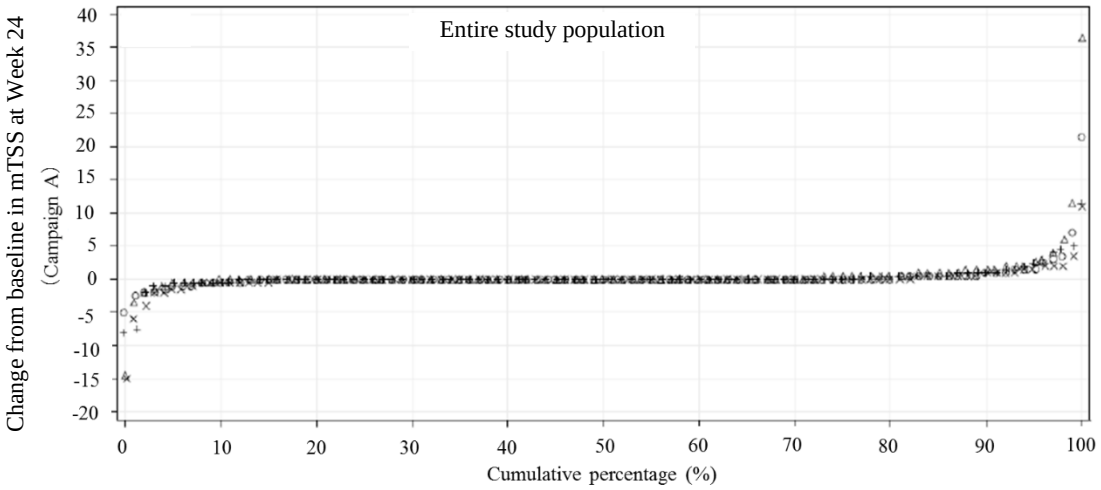
In the Japanese subpopulation of the FAS (71 subjects; 11 [100 mg + MTX], 23 [200 mg + MTX], 12 [200 mg alone], and 25 [MTX]), the incidence of study drug discontinuation up to Week 24 was 9.1% (1 of 11; "subject's decision") of subjects in the 100 mg + MTX group, 13.0% (3 of 23; "adverse events" in 3) of subjects in the 200 mg + MTX group, 8.3% (1 of 12; "adverse events") of subjects in the 200 mg alone group, and 4.0% (1 of 25; "subject's decision") of subjects in the MTX group.

The primary efficacy endpoint of ACR20 response at Week 24 and the change from baseline in mTSS are summarized in Table 52 and plotted in Figure 7. For both the 100 mg + MTX and 200 mg + MTX groups, the difference versus MTX alone was statistically significant for the ACR20. However, in a comparison of the change from baseline in mTSS, the difference from MTX alone was not statistically significant for either of the groups. Table 52 and Figure 8 show the results for the Japanese subpopulation.

Table 52. Results for the primary efficacy endpoint (FAS)

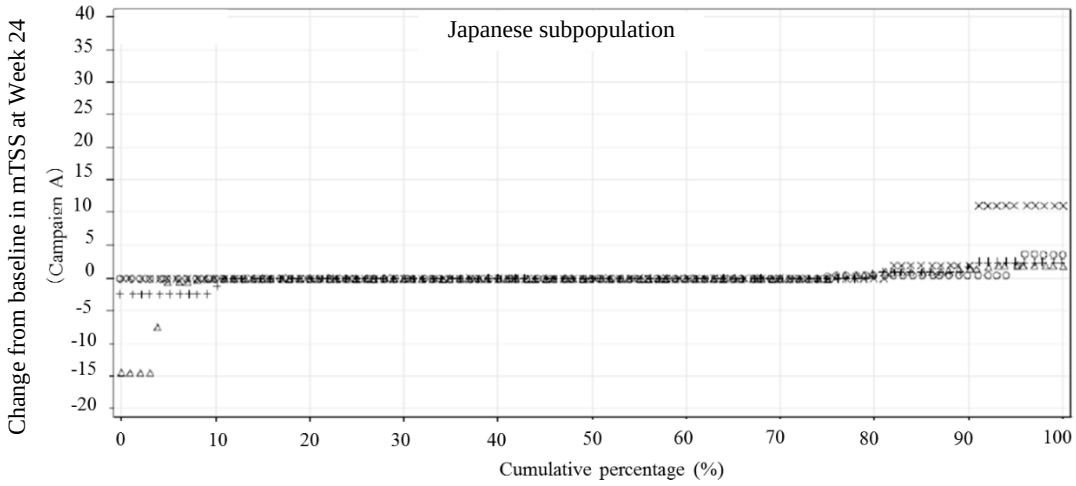
		100 mg + MTX	200 mg + MTX	200 mg alone	MTX
Entire study population	ACR20 at Week 24	80.2 (166/207)	81.0 (337/416)	78.1 (164/210)	71.4 (297/416)
	Difference from MTX [95% CI] *P*-value[a), c)]	8.8 [1.5, 16.1] 0.017	9.6 [3.6, 15.6] <0.001	6.7 [−0.7, 14.1] —	
	Change from baseline in mTSS at Week 24	0.22 ± 1.53 (184)	0.21 ± 1.68 (355)	−0.04 ± 1.71 (173)	0.51 ± 2.89 (356)
	Difference from MTX [95% CI][b)] *P*-value[b), c)]	−0.29 [−0.67, 0.10] —	−0.29 [−0.61, 0.02] 0.068	−0.55 [−0.94, −0.16] —	
Japanese subpopulation	ACR20 at Week 24	90.9 (10/11)	82.6 (19/23)	83.3 (10/12)	80.0 (20/25)
	Difference from MTX [95% CI]	10.9 [−18.8, 40.6]	2.6 [−23.6, 28.8]	3.3 [−29.1, 35.8]	
	Change from baseline in mTSS at Week 24	0.11 ± 1.20 (10)	0.28 ± 0.79 (20)	1.18 ± 3.31 (11)	−0.28 ± 3.04 (25)
	Difference from MTX [95% CI][b)]	0.40 [−1.42, 2.22]	0.54 [−0.91, 2.00]	1.45 [−0.31, 3.21]	

ACR20, % (n/N); change from baseline in mTSS, mean ± standard deviation (number of subjects evaluated)
For ACR20, missing data were imputed by NRI.
a) A logistic regression model using treatment, geographical region, and result (positive vs. negative) for anti-CCP antibodies or RF at screening as covariates
b) An MMRM model using treatment, visit, treatment by visit interaction, geographical region, result (positive vs. negative) for anti-CCP antibodies or RF at screening, and baseline values as covariates, assuming an unstructured covariance structure between timepoints (for the Japanese subpopulation analysis, geographical region and result [positive vs. negative] for anti-CCP antibodies or RF at screening were not included in the modeling)
c) Using a two-sided significance level of 5%, the multiplicity of hypothesis tests was adjusted according to the closed testing procedure in the order of 200 mg + MTX versus MTX and then 100 mg + MTX versus MTX for ACR20, and 200 mg + MTX versus MTX and then 100 mg + MTX versus MTX for change from baseline in mTSS.



○, 200 mg + MTX group; +, 100 mg + MTX group; ×, 200 mg alone group; Δ, MTX group

Figure 7. Cumulative probability distribution plot for change from baseline in mTSS at Week 24 (entire study population)



○, 200 mg + MTX group; +, 100 mg + MTX group; ×, 200 mg alone group; Δ, MTX group

Figure 8. Cumulative probability distribution plot for change from baseline in mTSS at Week 24 (Japanese subpopulation)

The incidence of adverse events was 79.2% (164 of 207) of subjects in the 100 mg + MTX group, 76.4% (318 of 416) of subjects in the 200 mg + MTX group, 68.1% (143 of 210) of subjects in the 200 mg alone group, and 73.3% (305 of 416) of subjects in the MTX group. Table 53 shows major adverse events.

Death occurred in 1 of 207 subjects (0.5%) in the 100 mg + MTX group (vertebral artery aneurysm/intracranial aneurysm) and 3 of 416 subjects (0.7%) in the 200 mg + MTX group (death,[26)] interstitial lung disease, and lupus myocarditis). A causal relationship to the study drug could not be ruled out for interstitial lung disease in the 200 mg + MTX group.

The incidence of serious adverse events was 6.3% (13 of 207) of subjects in the 100 mg + MTX group, 6.3% (26 of 416) of subjects in the 200 mg + MTX group, 8.1% (17 of 210) of subjects in the 200 mg alone group,

and 6.7% (28 of 416) of subjects in the MTX group. Among the serious adverse events, a causal relationship to the study drug could not be ruled out for the following events: accidental overdose/white blood cell count decreased and pancytopenia in the 100 mg + MTX group; pneumonia in 2 subjects, interstitial lung disease, lower respiratory tract infection, abdominal pain upper, megacolon, pneumonitis, subarachnoid haemorrhage in the 200 mg + MTX group; bone marrow failure, herpes zoster, lymphangitis, lung consolidation in the 200 mg alone group; pulmonary embolism, small cell lung cancer, pneumocystis jirovecii pneumonia, pneumonia, atrial fibrillation, atrial fibrillation, gastritis, sepsis, pneumonia cryptococcal in the MTX group.

The incidence of adverse events leading to study drug discontinuation was 6.3% (13 of 207) of subjects in the 100 mg + MTX group, 6.7% (28 of 416) of subjects in the 200 mg + MTX group, 2.4% (5 of 210) of subjects in the 200 mg alone group, and 6.0% (25 of 416) of subjects in the MTX group.

The incidence of adverse reactions was 49.8% (103 of 207) of subjects in the 100 mg + MTX group, 43.8% (182 of 416) of subjects in the 200 mg + MTX group, 27.1% (57 of 210) of subjects in the 200 mg alone group, and 42.1% (175 of 416) of subjects in the MTX group.

Table 53. Adverse events occurring in ≥3% of subjects in any group (safety analysis set)

Adverse event	100 mg + MTX (N = 207)	200 mg + MTX (N = 416)	200 mg alone (N = 210)	MTX (N = 416)
Nausea	35 (16.9)	51 (12.3)	15 (7.1)	50 (12.0)
Upper respiratory tract infection	9 (4.3)	42 (10.1)	14 (6.7)	34 (8.2)
Headache	8 (3.9)	23 (5.5)	8 (3.8)	25 (6.0)
ALT increased	6 (2.9)	23 (5.5)	3 (1.4)	11 (2.6)
Hypertension	10 (4.8)	22 (5.3)	15 (7.1)	14 (3.4)
Nasopharyngitis	17 (8.2)	21 (5.0)	17 (8.1)	25 (6.0)
Urinary tract infection	13 (6.3)	19 (4.6)	11 (5.2)	11 (2.6)
Alopecia	15 (7.2)	17 (4.1)	4 (1.9)	20 (4.8)
Diarrhoea	12 (5.8)	17 (4.1)	6 (2.9)	21 (5.0)
Abdominal pain upper	6 (2.9)	16 (3.8)	6 (2.9)	4 (1.0)
AST increased	2 (1.0)	15 (3.6)	4 (1.9)	7 (1.7)
Vomiting	7 (3.4)	14 (3.4)	3 (1.4)	11 (2.6)
Sinusitis	5 (2.4)	14 (3.4)	7 (3.3)	12 (2.9)
Dyspepsia	5 (2.4)	14 (3.4)	5 (2.4)	8 (1.9)
Leukopenia	4 (1.9)	13 (3.1)	1 (0.5)	6 (1.4)
Bronchitis	11 (5.3)	12 (2.9)	5 (2.4)	16 (3.8)
Cough	7 (3.4)	11 (2.6)	5 (2.4)	15 (3.6)
Abdominal pain	7 (3.4)	10 (2.4)	3 (1.4)	7 (1.7)
Back pain	6 (2.9)	10 (2.4)	3 (1.4)	14 (3.4)
Anaemia	5 (2.4)	7 (1.7)	2 (1.0)	16 (3.8)
Rheumatoid arthritis	7 (3.4)	4 (1.0)	0	14 (3.4)

n (%)

In the Japanese subpopulation, the incidence of adverse events was 90.9% (10 of 11) of subjects in the 100 mg + MTX group, 100% (23 of 23) of subjects in the 200 mg + MTX group, 91.7% (11 of 12) of subjects in the 200 mg alone group, and 80.0% (20 of 25) of subjects in the MTX group. Table 54 shows major adverse events.

No deaths occurred.

Serious adverse events occurred in 2 of 11 subjects (18.2%) in the 100 mg + MTX group (giant cell tumour of tendon sheath, appendiceal mucocoele), 2 of 23 subjects (8.7%) in the 200 mg + MTX group (pneumonia, pathological fracture), 3 of 12 subjects (25.0%) in the 200 mg alone group (bone marrow failure, cerebral artery

occlusion, herpes zoster), and 3 of 25 subjects (12.0%) in the MTX group (pulmonary embolism, small cell lung cancer, pneumocystis jirovecii pneumonia). Among the serious adverse events, a causal relationship to the study drug could not be ruled out for the following events: pneumonia in the 200 mg + MTX group; bone marrow failure and herpes zoster in the 200 mg alone group; pulmonary embolism, small cell lung cancer, pneumocystis jirovecii pneumonia in the MTX group.

The incidence of adverse events leading to study drug discontinuation was 13.0% (3 of 23) of subjects in the 200 mg + MTX group, 16.7% (2 of 12) of subjects in the 200 mg alone group, and 12.0% (3 of 25) of subjects in the MTX group.

The incidence of adverse reactions was 63.6% (7 of 11) of subjects in the100 mg + MTX group, 73.9% (17 of 23) of subjects in the 200 mg + MTX group, 58.3% (7 of 12) of subjects in the 200 mg alone group, and 76.0% (19 of 25) of subjects in the MTX group.

Table 54. Adverse events occurring in ≥3 subjects in any group (safety analysis set, Japanese subpopulation)

Adverse event	100 mg + MTX (N = 11)	200 mg + MTX (N = 23)	200 mg alone (N = 12)	MTX (N = 25)
Nasopharyngitis	2 (18.2)	6 (26.1)	5 (41.7)	10 (40.0)
Hepatic enzyme increased	0	4 (17.4)	1 (8.3)	0
Nausea	1 (9.1)	3 (13.0)	1 (8.3)	5 (20.0)
Abdominal discomfort	1 (9.1)	3 (13.0)	1 (8.3)	4 (16.0)
Hepatic function abnormal	0	2 (8.7)	0	3 (12.0)
Stomatitis	1 (9.1)	0	0	5 (20.0)
Bronchitis	0	0	0	5 (20.0)

n (%)

7.1.4 Global long-term extension study (CTD 5.3.5.1.9, 5.3.5.1.12, and 5.3.5.1.13, Study GS-US-417-0304 [the FINCH4 study] [ongoing since February 2017, data cut-off in September 2019])

A double-blind, parallel group study was conducted to assess the long-term safety and efficacy of filgotinib in patients with RA[31)] who had completed one of the parent studies (the FINCH1, FINCH2, or FINCH3 studies) in 32 countries or regions including Japan, the US, Poland, and Mexico.

Subjects who had been receiving filgotinib maleate in the parent study were to continue the same filgotinib maleate regimen in combination with cDMARDs[32)] that were allowed in the parent study. Subjects who had been receiving a study drug other than filgotinib maleate at the last visit in the parent study, and subjects who had been receiving standard of care for RA (the FINCH2 study only) were to receive filgotinib maleate 100 mg or 200 mg orally once daily for up to 3 years.[33)]

Of 2,731 subjects entered in the extension study, those who received at least 1 dose of the study drug (2,729 subjects; 1,199 [100 mg] and 1,530 [200 mg]) were included in the safety analysis set. The incidence of study drug discontinuation was 10.3% (123 of 1,199) of subjects in the 100 mg group and 8.8% (135 of 1,530) of

31) Subjects who were discontinued from study drug treatment due to inadequate response and had received standard of care for RA in the FINCH1 study or the FINCH3 study were excluded.
32) Subjects from the FINCH3 study were to discontinue treatment with MTX or placebo-to-match MTX. The combined use of cDMARDs was allowed after ≥4 weeks from discontinuation of MTX/placebo.
33) Three years, the market launch of filgotinib, or discontinuation of filgotinib maleate development, whichever would occur first.

subjects in the 200 mg group. Major reasons for discontinuation included “adverse events” (3.4% [41 of 1,199] of subjects in the 100 mg group and 3.1% [47 of 1,530] of subjects in the 200 mg group) and “subject’s decision” (3.7% [44 of 1,199] of subjects in the 100 mg group and 2.7% [41 of 1,530] of subjects in the 200 mg group).

In the Japanese subpopulation of the safety analysis set (207 subjects; 97 [100 mg] and 110 [200 mg]), the incidence of study drug discontinuation was 8.2% (8 of 97) of subjects in the 100 mg group and 8.2% (9 of 110) of subjects in the 200 mg group. Major reasons for discontinuation included “adverse events” (4.1% [4 of 97] of subjects in the 100 mg group and 5.5% [6 of 110] of subjects in the 200 mg group) and “pregnancy” (1.0% [1 of 97] of subjects in the 100 mg group and 1.8% [2 of 110] of subjects in the 200 mg group).

No analysis has been performed for efficacy using the submitted data with the cut-off date.

The incidence of adverse events was 62.1% (745 of 1,199) of subjects in the 100 mg group and 61.8% (946 of 1,530) of subjects in the 200 mg group. Table 55 shows major adverse events.

Death occurred in 3 of 1,199 subjects (0.3%) in the 100 mg group (malignant peritoneal neoplasm/ovarian cancer, cardiac arrest, and cardiopulmonary failure in 1 subject each) and 9 of 1,530 subjects (0.6%) in the 200 mg group (ischaemic stroke, lung adenocarcinoma, acute myocardial infarction, pneumonia/septic shock/electrolyte imbalance/acute kidney injury, oesophageal squamous cell carcinoma metastatic, staphylococcal sepsis, cardiac failure, pericarditis, and cerebrovascular accident in 1 subject each). Among these events, a causal relationship to the study drug could not be ruled out for acute myocardial infarction, pneumonia/septic shock, oesophageal squamous cell carcinoma metastatic, and staphylococcal sepsis in the 200 mg group.

Serious adverse events occurred in 97 of 1,199 subjects (8.1%) in the 100 mg group and 115 of 1,530 subjects (7.5%) in the 200 mg group. Among the serious adverse events, a causal relationship to the study drug could not be ruled out for the following events: in the 100 mg group, pneumonia in 2 subjects, abortion spontaneous in 2 subjects, oesophageal carcinoma, pyelonephritis, adenocarcinoma pancreas, pyelonephritis acute, pneumonia/pneumonia, pulmonary embolism, non-cardiac chest pain/dyspnoea/bronchitis/cellulitis, coronary artery disease, postmenopausal haemorrhage/endometrial cancer, anaemia, ventricular extrasystoles, acute myocardial infarction, cataract, pancreatitis acute, bronchitis/meningitis tuberculous/pulmonary tuberculosis, cellulitis/urinary tract infection bacterial, overlap syndrome/lower respiratory tract infection/lymph node tuberculosis, lymph gland infection, pancreatitis/pancreatitis acute; in the 200 mg group, pneumonia in 2 subjects, acute myocardial infarction in 2 subjects, herpes zoster in 2 subjects, pulmonary embolism in 2 subjects, gastric cancer, herpes zoster disseminated, tonsillitis, diverticulitis, pyelonephritis chronic, sepsis/pneumonia, cholecystitis acute, hyperamylasaemia/hyperlipasaemia, abortion spontaneous incomplete, pneumonia/septic shock, pulmonary embolism/deep vein thrombosis, oesophageal squamous cell carcinoma metastatic, arthritis bacterial, pyelonephritis acute, angina unstable, pneumonitis/acute respiratory failure, non-cardiac chest pain, hepatitis, mastoiditis/meningitis pneumococcal/subdural empyema, extradural abscess/osteomyelitis/paraspinal abscess/staphylococcal sepsis/localised infection, stress cardiomyopathy,

malignant neoplasm of unknown primary site, seborrhoeic dermatitis/seborrhoeic dermatitis, gastritis erosive/haemorrhagic erosive gastritis, gastric perforation, ischaemic stroke, bladder neoplasm, cervix carcinoma, pneumonia pneumococcal, conjunctival melanoma, cellulitis/cellulitis, cellulitis, osteonecrosis.

The incidence of study drug discontinuation was 3.5% (42 of 1,199) of subjects in the 100 mg group and 3.1% (47 of 1,530) of subjects in the 200 mg group.

The incidence of adverse reactions was 18.5% (222 of 1,199) of subjects in the 100 mg group and 19.3% (296 of 1,530) of subjects in the 200 mg group.

Table 55. Adverse events occurring in ≥2% of subjects in either group (safety analysis set)

Adverse event	100 mg (N = 1,199)	200 mg (N = 1,530)	Adverse event	100 mg (N = 1,199)	200 mg (N = 1,530)
Nasopharyngitis	74 (6.2)	91 (5.9)	Hypertension	32 (2.7)	41 (2.7)
Upper respiratory tract infection	57 (4.8)	78 (5.1)	Nausea	24 (2.0)	37 (2.4)
Urinary tract infection	47 (3.9)	67 (4.4)	Back pain	24 (2.0)	31 (2.0)
Rheumatoid arthritis	70 (5.8)	62 (4.1)	Herpes zoster	14 (1.2)	31 (2.0)
Bronchitis	34 (2.8)	53 (3.5)	Arthralgia	29 (2.4)	30 (2.0)
Latent tuberculosis	26 (2.2)	44 (2.9)	Headache	25 (2.1)	29 (1.9)

n (%)

In the Japanese subpopulation, the incidence of adverse events was 77.3% (75 of 97) of subjects in the 100 mg group and 80.0% (88 of 110) of subjects in the 200 mg group. Table 56 shows major adverse events.

No deaths occurred.

Serious adverse events occurred in 7 of 97 subjects (7.2%) in the 100 mg group (retinal detachment/retinal detachment, lumbar spinal stenosis, abortion spontaneous, oesophageal carcinoma, pneumonia, osteoarthritis, pyelonephritis) and 8 of 110 subjects (7.3%) in the 200 mg group (vertigo positional, gastric cancer, herpes zoster disseminated, cataract, tonsillitis, diverticulitis, pneumonia, cholecystitis acute). Among the serious adverse events, a causal relationship to the study drug could not be ruled out for the following events: abortion spontaneous, oesophageal carcinoma, pneumonia, pyelonephritis in the 100 mg group; gastric cancer, herpes zoster disseminated, tonsillitis, diverticulitis, and pneumonia in the 200 mg group.

The incidence of adverse events leading to study drug discontinuation was 4.1% (4 of 97) of subjects in the 100 mg group and 5.5% (6 of 110) of subjects in the 200 mg group.

The incidence of adverse reactions was 37.1% (36 of 97) of subjects in the 100 mg group and 34.5% (38 of 110) of subjects in the 200 mg group.

Table 56. Adverse events occurring in ≥3% of subjects in either group (safety analysis set, Japanese subpopulation)

Adverse event	100 mg (N = 97)	200 mg (N = 110)	Adverse event	100 mg (N = 97)	200 mg (N = 110)
Nasopharyngitis	17 (17.5)	25 (22.7)	Vomiting	1 (1.0)	4 (3.6)
Rheumatoid arthritis	12 (12.4)	10 (9.1)	Pyrexia	0	4 (3.6)
Fall	4 (4.1)	7 (6.4)	Dental caries	3 (3.1)	3 (2.7)
Nausea	7 (7.2)	4 (3.6)	Hyperkeratosis	3 (3.1)	3 (2.7)
Back pain	2 (2.1)	4 (3.6)	Dyslipidaemia	4 (4.1)	2 (1.8)
Tinea pedis	2 (2.1)	4 (3.6)	Upper respiratory tract infection	4 (4.1)	2 (1.8)
Bronchitis	1 (1.0)	4 (3.6)	Myalgia	3 (3.1)	2 (1.8)
Cystitis	1 (1.0)	4 (3.6)	Limb injury	3 (3.1)	0
Hepatic function abnormal	1 (1.0)	4 (3.6)	Lumbar spinal stenosis	3 (3.1)	0

n (%)

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan for filgotinib:

Diagnostic and treatment algorithms for RA in the treatment guidelines issued in Japan, Europe, and the US are generally similar, and the treatment system for RA in Japan does not differ significantly from those of the US and European countries. In addition, the pharmacokinetic profiles of FILGOTINIB in healthy subjects in the phase I study showed no significant differences between Japanese and non-Japanese groups [see Section 6.2.1.1]. Results of the foreign phase II studies in patients with RA who had an inadequate response to MTX suggested that FILGOTINIB has efficacy in terms of improving the ACR20. Therefore, it was considered that the efficacy and safety of filgotinib maleate in Japanese patients with RA could be evaluated by having them participate in the global phase III studies, in which more than one dose level would be selected based on the results of the foreign phase II studies. It was decided that the "study population and coadministered drug," "efficacy endpoint," and "dosage regimen" for the global phase III studies would be specified as shown below.

- Study population and coadministered drug

According to the recommendation in the RA treatment guidelines issued in Japan, Europe, and the US, treatment with anti-rheumatic drugs should be initiated immediately after diagnosis of RA is made, aiming to achieve/maintain clinical, structural, and functional remission, with the first-line drug being MTX. With the exception of patients intolerant to MTX, treatment with MTX alone or MTX in combination with other cDMARDs or low-dose corticosteroid is generally recommended. For patients who had an inadequate response to cDMARDs including MTX, the use of biologics or JAK inhibitors is recommended (*JCR RA Treatment Guidelines* 2014, *Arthritis Care Res.* 2016;68:1-25, and *Ann Rheum Dis.* 2020;0:1-15). On the basis of the above treatment system, global phase III studies were conducted in patients with moderately to severely active RA who had had an inadequate response to MTX (the FINCH1 study) or to biologics (the FINCH2 study) to confirm the efficacy and safety of filgotinib in combination with MTX or cDMARDs. Furthermore, with the expectation that filgotinib will become a treatment option for the early stage of RA, the FINCH3 study (global phase III) study was conducted to confirm the efficacy and safety of filgotinib alone or in combination with MTX in MTX-naïve patients with active RA.

- Efficacy endpoint

The efficacy of filgotinib in treating the clinical manifestations of RA was to be evaluated according to the following measures: ACR improvement, an assessment index utilized internationally, consisting of composite

measures including SJC, TJC, acute phase reactants such as CRP, patient global assessment of disease activity, patient assessment of pain, physician's global assessment of disease activity, functional status of daily living by Health Assessment Questionnaire-Disability Index (HAQ-DI); indices for improvement of disease activity based on disease activity score (DAS) and clinical disease activity index (CDAI).

The efficacy of filgotinib on structural damage of joints was to be evaluated using mTSS, the assessment index for structural joint damage.

- Dosage regimen

An exposure-response analysis based on data from the early phase II studies (Studies GLPG0634-CL-201 and -202) conducted in patients with active RA who had had an inadequate response to MTX, failed to demonstrate that doses >200 mg/day of FILGOTINIB resulted in increased clinically significant benefits compared with 200 mg/day. Accordingly, the maximum dose in clinical studies conducted thereafter was specified as FILGOTINIB 200 mg/day. In the late phase II study (Study GLPG0634-CL-203) conducted in patients with RA who had had an inadequate response to MTX, the efficacy and safety of filgotinib in combination with MTX were evaluated by ACR20 at Week 12 as the primary endpoint. In the FILGOTINIB 200-mg QD and 100-mg QD groups, the difference versus placebo was statistically significant while in the 50-mg QD group, there was no statistically significant difference in the comparison with placebo.

The above results indicated that the dosage regimen of phase III studies was determined to be filgotinib maleate 100 mg or 200 mg orally once daily.

PMDA accepted the applicant's explanation and concluded that the efficacy and safety of filgotinib in Japanese patients with RA can be evaluated based on the submitted clinical data package.

7.R.2 Efficacy

7.R.2.1 Efficacy in treating the clinical manifestations of RA

The applicant's explanation about the efficacy of filgotinib in reducing the clinical manifestations of RA:
In the clinical studies in patients with RA who had an inadequate response to MTX (the FINCH1 study), biologics (the FINCH2 study), or were MTX-naïve (the FINCH3 study), the difference versus placebo in ACR20 at Week 12 or 24, the primary endpoint, was statistically significant both in the 100 mg and 200 mg groups, demonstrating the superiority of filgotinib maleate 100 mg and 200 mg over placebo [see Sections 7.1.1 through 7.1.3]. The results of the Japanese subpopulation in each study tended to be similar to those of the entire study population [see Sections 7.1.1 through 7.1.3].

Table 57 shows the efficacy endpoint data relating to the clinical manifestations of RA at the time of primary endpoint evaluation (Week 12 or 24) in the FINCH1, FINCH2, and FINCH3 studies. The results showed consistent efficacy in the 100 mg and 200 mg groups independent of patient population or endpoint.

Table 57. The efficacy results for clinical manifestations of RA (FAS, NRI)

Study	FINCH1		FINCH2		FINCH3	
Patient population	MTX-inadequate responder (IR)		Biologic-IR		MTX-naïve	
Coadministered drug	MTX		cDMARDs		MTX	
Primary evaluation timepoint	Week 12		Week 12		Week 24	
Study population	Entire study population	Japanese subpopulation	Entire study population	Japanese subpopulation	Entire study population	Japanese subpopulation
ACR20 (primary endpoint)						
100 mg	69.8 (335/480)	65.9 (27/41)	57.5 (88/153)	53.3 (8/15)	80.2 (166/207)	90.9 (10/11)
200 mg	76.6 (364/475)	77.5 (31/40)	66.0 (97/147)	83.3 (10/12)	81.0 (337/416)	82.6 (19/23)
Adalimumab	70.5 (229/325)	53.6 (15/28)	—	—	—	—
Placebo	49.9 (237/475)	36.8 (14/38)	31.1 (46/148)	30.8 (4/13)	71.4 (297/416)	80.0 (20/25)
200 mg alone[a)]	—	—	—	—	78.1 (164/210)	83.3 (10/12)
ACR50						
100 mg	36.5 (175/480)	46.3 (19/41)	32.0 (49/153)	20.0 (3/15)	57.0 (118/207)	90.9 (10/11)
200 mg	47.2 (224/475)	57.5 (23/40)	42.9 (63/147)	33.3 (4/12)	61.5 (256/416)	73.9 (17/23)
Adalimumab	35.1 (114/325)	32.1 (9/28)	—	—	—	—
Placebo	19.8 (94/475)	7.9 (3/38)	14.9 (22/148)	0 (0/13)	45.7 (190/416)	64.0 (16/25)
200 mg alone[a)]	—	—	—	—	58.1 (122/210)	66.7 (8/12)
ACR70						
100 mg	18.5 (89/480)	26.8 (11/41)	14.4 (22/153)	6.7 (1/15)	40.1 (83/207)	45.5 (5/11)
200 mg	26.1 (124/475)	35.0 (14/40)	21.8 (32/147)	16.7 (2/12)	43.8 (182/416)	56.5 (13/23)
Adalimumab	14.2 (46/325)	10.7 (3/28)	—	—	—	—
Placebo	6.7 (32/475)	2.6 (1/38)	6.8 (10/148)	0 (0/13)	26.0 (108/416)	40.0 (10/25)
200 mg alone[a)]	—	—	—	—	40.0 (84/210)	50.0 (6/12)
Proportion of subjects achieving DAS28-CRP ≤3.2						
100 mg	38.8 (186/480)	56.1 (23/41)	37.3 (57/153)	46.7 (7/15)	62.8 (130/207)	90.9 (10/11)
200 mg	49.7 (236/475)	70.0 (28/40)	40.8 (60/147)	66.7 (8/12)	68.8 (286/416)	73.9 (17/23)
Adalimumab	43.4 (141/325)	60.7 (17/28)	—	—	—	—
Placebo	23.4 (111/475)	18.4 (7/38)	15.5 (23/148)	0 (0/13)	46.2 (192/416)	56.0 (14/25)
200 mg alone[a)]	—	—	—	—	60.0 (126/210)	58.3 (7/12)
Proportion of subjects achieving DAS28-CRP <2.6						
100 mg	23.8 (114/480)	39.0 (16/41)	25.5 (39/153)	26.7 (4/15)	42.5 (88/207)	63.6 (7/11)
200 mg	34.1 (162/475)	52.5 (21/40)	22.4 (33/147)	41.7 (5/12)	54.1 (225/416)	69.6 (16/23)
Adalimumab	23.7 (77/325)	42.9 (12/28)	—	—	—	—
Placebo	9.3 (44/475)	5.3 (2/38)	8.1 (12/148)	0 (0/13)	29.1 (121/416)	40.0 (10/25)
200 mg alone[a)]	—	—	—	—	42.4 (89/210)	50.0 (6/12)
Proportion of subjects achieving CDAI ≤2.8						
100 mg	11.0 (53/480)	4.9 (2/41)	11.1 (17/153)	6.7 (1/15)	27.1 (56/207)	36.4 (4/11)
200 mg	12.4 (59/475)	22.5 (9/40)	12.2 (18/147)	16.7 (2/12)	26.2 (109/416)	30.4 (7/23)
Adalimumab	5.8 (19/325)	10.7 (3/28)	—	—	—	—
Placebo	2.7 (13/475)	2.6 (1/38)	5.4 (8/148)	0 (0/13)	13.0 (54/416)	8.0 (2/25)
200 mg alone[a)]	—	—	—	—	21.4 (45/210)	33.3 (4/12)
Proportion of subjects meeting ACR/EULAR Boolean remission criteria						
100 mg	6.5 (31/480)	4.9 (2/41)	6.5 (10/153)	6.7 (1/15)	21.3 (44/207)	36.4 (4/11)
200 mg	9.5 (45/475)	20.0 (8/40)	9.5 (14/147)	16.7 (2/12)	22.8 (95/416)	39.1 (9/23)
Adalimumab	5.2 (17/325)	14.3 (4/28)	—	—	—	—
Placebo	1.9 (9/475)	2.6 (1/38)	2.7 (4/148)	0 (0/13)	11.3 (47/416)	12.0 (3/25)
200 mg alone[a)]	—	—	—	—	18.1 (38/210)	25.0 (3/12)

% (n/N); —, not specified
For the FINCH3 study, the 100 mg group, 200 mg group, and placebo group shown above represent the 100 mg + MTX group, 200 mg + MTX group, and MTX group in Section 7.1.3, respectively (the same shall apply for the treatment groups in Table 58, Table 59, Table 60, and Table 78).
a) MTX was not coadministered.

Table 58 shows the results of subgroup analysis by patient characteristics for the primary endpoint of the FINCH1, FINCH2, and FINCH3 studies. There were no clear differences in the efficacy of filgotinib between the subgroups.

Table 58. Results of efficacy endpoints by patient characteristics (FAS, NRI)

Study		FINCH1				FINCH2			FINCH3			
Patient population		MTX-IR				Biologic-IR			MTX-naïve			
Primary endpoint		ACR20 at Week 12				ACR20 at Week 12			ACR20 at Week 24			
Coadministered drug		MTX				cDMARDs			MTX			None
Treatment group		100 mg	200 mg	Adalimumab	Placebo	100 mg	200 mg	Placebo	100 mg	200 mg	Placebo	200 mg alone
Sex	Female	68.7 (274/399)	76.3 (289/379)	71.4 (190/266)	49.6 (194/391)	58.8 (70/119)	68.3 (82/120)	32.2 (39/121)	81.0 (128/158)	83.1 (270/325)	72.8 (227/312)	77.7 (129/166)
	Male	75.3 (61/81)	78.1 (75/96)	66.1 (39/59)	51.2 (43/84)	52.9 (18/34)	55.6 (15/27)	25.9 (7/27)	77.6 (38/49)	73.6 (67/91)	67.3 (70/104)	79.5 (35/44)
Age	<65 years	69.3 (268/387)	77.9 (310/398)	71.3 (184/258)	50.5 (192/380)	54.7 (64/117)	64.3 (72/112)	31.1 (33/106)	81.0 (136/168)	83.3 (274/329)	69.9 (230/329)	80.6 (137/170)
	≥65 years	72.0 (67/93)	70.1 (54/77)	67.2 (45/67)	47.4 (45/95)	66.7 (24/36)	71.4 (25/35)	31.0 (13/42)	76.9 (30/39)	72.4 (63/87)	77.0 (67/87)	67.5 (27/40)
Body weight	<60 kg	66.4 (95/143)	82.7 (115/139)	64.8 (57/88)	41.3 (57/138)	65.2 (15/23)	82.6 (19/23)	35.5 (11/31)	86.7 (39/45)	84.8 (89/105)	74.2 (72/97)	83.0 (44/53)
	≥60 kg <100 kg	70.7 (220/311)	74.4 (221/297)	73.9 (156/211)	54.0 (167/309)	55.6 (55/99)	65.3 (64/98)	29.3 (29/99)	78.7 (111/141)	80.9 (220/272)	71.5 (193/270)	79.7 (114/143)
	≥100 kg	76.9 (20/26)	71.8 (28/39)	61.5 (16/26)	46.4 (13/28)	58.1 (18/31)	53.8 (14/26)	33.3 (6/18)	76.2 (16/21)	71.8 (28/39)	65.3 (32/49)	42.9 (6/14)
RA duration	<5 years (<1 year)	71.8 (158/220)	77.9 (187/240)	68.8 (106/154)	51.1 (120/235)	42.9 (12/28)	57.1 (20/35)	32.4 (11/34)	79.7 (110/138)	80.3 (216/269)	72.3 (204/282)	78.8 (108/137)
	≥5 years (≥1 year)	68.1 (177/260)	75.3 (177/235)	71.9 (123/171)	48.8 (117/240)	60.8 (76/125)	68.8 (77/112)	30.7 (35/114)	81.2 (56/69)	82.3 (121/147)	69.4 (93/134)	76.7 (56/73)
Prior biologic treatment	Yes	43.8 (7/16)	64.7 (11/17)	75.0 (6/8)	83.3 (5/6)							
	No	70.7 (328/464)	77.1 (353/458)	70.3 (223/317)	49.5 (232/469)							
Oral corticosteroid use	Yes	67.2 (154/229)	77.7 (178/229)	72.9 (102/140)	55.3 (120/217)	55.9 (38/68)	66.2 (45/68)	23.9 (17/71)	84.1 (74/88)	78.3 (112/143)	72.4 (126/174)	76.4 (68/89)
	No	72.1 (181/251)	75.6 (186/246)	68.6 (127/185)	45.3 (117/258)	58.8 (50/85)	65.8 (52/79)	37.7 (29/77)	77.3 (92/119)	82.4 (225/273)	70.7 (171/242)	79.3 (96/121)
DAS28 -CRP	≤5.1	67.2 (82/122)	77.4 (82/106)	64.9 (48/74)	43.8 (56/128)	55.9 (19/34)	69.7 (23/33)	28.6 (8/28)	82.5 (52/63)	84.7 (105/124)	66.7 (70/105)	82.4 (42/51)
	>5.1	70.7 (253/358)	76.4 (282/369)	72.1 (181/251)	52.2 (181/347)	58.0 (69/119)	64.9 (74/114)	31.7 (38/120)	79.2 (114/144)	79.5 (232/292)	73.0 (227/311)	76.7 (122/159)
RF or anti-CCP antibodies	Positive	70.1 (288/411)	78.3 (314/401)	73.5 (202/275)	49.5 (203/410)	61.0 (72/118)	68.8 (77/112)	31.0 (35/113)	83.3 (135/162)	83.9 (266/317)	72.7 (234/322)	81.0 (128/158)
	Negative	68.1 (47/69)	67.6 (50/74)	54.0 (27/50)	52.3 (34/65)	45.7 (16/35)	57.1 (20/35)	31.4 (11/35)	68.9 (31/45)	71.7 (71/99)	67.0 (63/94)	69.2 (36/52)

% (n/N)
RA duration, <5 years vs. ≥5 years (the FINCH1 and FINCH2 studies); <1 year vs. ≥1 year (the FINCH3 study)

Table 59 shows the results of long-term treatment with filgotinib. In all studies, efficacy observed at the primary evaluation timepoint was maintained at subsequent timepoints.

Table 59. The results of efficacy endpoints in long-term treatment with filgotinib (FAS, NRI)

Study	FINCH1		FINCH2		FINCH3	
Patient population	MTX-IR		Biologic-IR		MTX-naïve	
Coadministered drug	MTX		cDMARDs		MTX	
Evaluation timepoint	Week 52		Week 24		Week 52	
Study population	Entire study population	Japanese subpopulation	Entire study population	Japanese subpopulation	Entire study population	Japanese subpopulation
ACR20						
100 mg	75.6 (363/480)	85.4 (35/41)	54.9 (84/153)	60.0 (9/15)	73.4 (152/207)	81.8 (9/11)
200 mg	78.3 (372/475)	75.0 (30/40)	69.4 (102/147)	91.7 (11/12)	75.0 (312/416)	82.6 (19/23)
200 mg alone[a)]	—	—	—	—	74.8 (157/210)	75.0 (9/12)
Adalimumab	73.5 (239/325)	67.9 (19/28)	—	—	—	—
Placebo	—	—	34.5 (51/148)	15.4 (2/13)	61.8 (257/416)	76.0 (19/25)
Placebo-100 mg	83.8 (160/191)	84.6 (11/13)	—	—	—	—
Placebo-200 mg	82.6 (157/190)	83.3 (10/12)	—	—	—	—
ACR50						
100 mg	58.5 (281/480)	61.0 (25/41)	35.3 (54/153)	26.7 (4/15)	59.4 (123/207)	72.7 (8/11)
200 mg	62.3 (296/475)	57.5 (23/40)	45.6 (67/147)	58.3 (7/12)	62.3 (259/416)	82.6 (19/23)
200 mg alone[a)]	—	—	—	—	61.4 (129/210)	58.3 (7/12)
Adalimumab	59.1 (192/325)	42.9 (12/28)	—	—	—	—
Placebo	—	—	18.9 (28/148)	0 (0/13)	48.3 (201/416)	68.0 (17/25)
Placebo-100 mg	64.9 (124/191)	69.2 (9/13)	—	—	—	—
Placebo-200 mg	65.8 (125/190)	75.0 (9/12)	—	—	—	—
ACR70						
100 mg	37.5 (180/480)	39.0 (16/41)	20.3 (31/153)	26.7 (4/15)	40.1 (83/207)	63.6 (7/11)
200 mg	44.2 (210/475)	40.0 (16/40)	32.0 (47/147)	25.0 (3/12)	47.8 (199/416)	69.6 (16/23)
200 mg alone[a)]	—	—	—	—	45.2 (95/210)	25.0 (3/12)
Adalimumab	39.4 (128/325)	17.9 (5/28)	—	—	—	—
Placebo	—	—	8.1 (12/148)	0 (0/13)	29.8 (124/416)	32.0 (8/25)
Placebo-100 mg	36.6 (70/191)	38.5 (5/13)	—	—	—	—
Placebo-200 mg	46.3 (88/190)	33.3 (4/12)	—	—	—	—
Proportion of subjects achieving DAS28-CRP ≤3.2						
100 mg	59.4 (285/480)	73.2 (30/41)	37.9 (58/153)	46.7 (7/15)	59.9 (124/207)	90.9 (10/11)
200 mg	65.9 (313/475)	75.0 (30/40)	48.3 (71/147)	75.0 (9/12)	69.0 (287/416)	82.6 (19/23)
200 mg alone[a)]	—	—	—	—	65.7 (138/210)	75.0 (9/12)
Adalimumab	58.8 (191/325)	67.9 (19/28)	—	—	—	—
Placebo	—	—	20.9 (31/148)	0 (0/13)	47.6 (198/416)	60.0 (15/25)
Placebo-100 mg	66.0 (126/191)	76.9 (10/13)	—	—	—	—
Placebo-200 mg	67.9 (129/190)	91.7 (11/12)	—	—	—	—
Proportion of subjects achieving DAS28-CRP <2.6						
100 mg	42.9 (206/480)	51.2 (21/41)	26.1 (40/153)	26.7 (4/15)	43.0 (89/207)	81.8 (9/11)
200 mg	53.9 (256/475)	65.0 (26/40)	30.6 (45/147)	50.0 (6/12)	53.4 (222/416)	73.9 (17/23)
200 mg alone[a)]	—	—	—	—	46.2 (97/210)	50.0 (6/12)
Adalimumab	46.2 (150/325)	60.7 (17/28)	—	—	—	—
Placebo	—	—	12.2 (18/148)	0 (0/13)	31.5 (131/416)	48.0 (12/25)
Placebo-100 mg	50.3 (96/191)	53.8 (7/13)	—	—	—	—
Placebo-200 mg	49.5 (94/190)	66.7 (8/12)	—	—	—	—
Proportion of subjects achieving CDAI ≤2.8						
100 mg	24.2 (116/480)	22.0 (9/41)	15.7 (24/153)	13.3 (2/15)	28.5 (59/207)	63.6 (7/11)
200 mg	29.5 (140/475)	27.5 (11/40)	19.0 (28/147)	25.0 (3/12)	34.9 (145/416)	60.9 (14/23)
200 mg alone[a)]	—	—	—	—	26.2 (55/210)	25.0 (3/12)
Adalimumab	22.8 (74/325)	7.1 (2/28)	—	—	—	—
Placebo	—	—	6.1 (9/148)	0 (0/13)	17.3 (72/416)	16.0 (4/25)
Placebo-100 mg	25.7 (49/191)	23.1 (3/13)	—	—	—	—
Placebo-200 mg	28.4 (54/190)	25.0 (3/12)	—	—	—	—
Proportion of subjects meeting ACR/EULAR Boolean remission criteria						
100 mg	19.2 (92/480)	22.0 (9/41)	10.5 (16/153)	13.3 (2/15)	22.7 (47/207)	45.5 (5/11)
200 mg	22.5 (107/475)	30.0 (12/40)	10.9 (16/147)	8.3 (1/12)	28.8 (120/416)	56.5 (13/23)
200 mg alone[a)]	—	—	—	—	17.1 (36/210)	16.7 (2/12)
Adalimumab	16.9 (55/325)	10.7 (3/28)	—	—	—	—
Placebo	—	—	4.1 (6/148)	0 (0/13)	12.7 (53/416)	16.0 (4/25)
Placebo-100 mg	16.2 (31/191)	15.4 (2/13)	—	—	—	—
Placebo-200 mg	16.8 (32/190)	16.7 (2/12)	—	—	—	—

% (n/N); —, not specified

a) MTX was not coadministered.

The above results indicate that the efficacy of filgotinib in reducing the clinical manifestations of RA has been demonstrated.

PMDA accepted the applicant's explanation and concluded that the efficacy of filgotinib in reducing the clinical manifestations of RA has been demonstrated.

7.R.2.2 Inhibition of structural joint damage

The applicant's explanation about the efficacy of filgotinib in inhibiting structural damage to the joint:
In the global phase III studies in patients with RA who had an inadequate response to MTX (the FINCH1 study) or were MTX-naïve (the FINCH3 study), the change from baseline in mTSS at Week 24 was specified as the primary endpoint, and the efficacy of filgotinib in inhibiting structural joint damage was investigated.

Table 60 shows the change from baseline in mTSS and the proportion of subjects who had radiographic evidence of no structural damage progression (mTSS ≤0) at Week 24 and at Week 52 in the FINCH1 and FINCH3 studies.

Table 60. Change from baseline in mTSS and proportion of subjects who had radiographic evidence of no structural damage progression (FAS)

	Study	FINCH1				FINCH3			
	Patient population	MTX-IR				MTX-naïve			
	Coadministered drug	MTX				MTX			None
	Treatment	100 mg	200 mg	ADA	Placebo	100 mg	200 mg	Placebo	200 mg alone
Week 24	Entire study population								
	Change from baseline in mTSS (*)	0.17 ± 0.91 (404)	0.13 ± 0.94 (405)	0.16 ± 0.95 (271)	0.37 ± 1.42 (351)	0.22 ± 1.53 (184)	0.21 ± 1.68 (355)	0.51 ± 2.89 (356)	−0.04 ± 1.71 (173)
	Difference from placebo [95% CI][a)]	−0.25 [−0.40, −0.10]	−0.27 [−0.43, −0.12]			−0.29 [−0.67, 0.10]	−0.29 [−0.61, 0.02]		−0.55 [−0.94, −0.16]
	Subjects with mTSS ≤0 (NRI)	72.3 (347/480)	74.9 (356/475)	72.0 (234/325)	59.8 (284/475)	68.1 (141/207)	68.8 (286/416)	62.0 (258/416)	68.1 (143/210)
	Japanese subpopulation								
	Change from baseline in mTSS	0.13 ± 0.92 (36)	0.72 ± 2.43 (36)	0.20 ± 0.50 (22)	0.42 ± 1.39 (25)	0.11 ± 1.20 (10)	0.28 ± 0.79 (20)	−0.28 ± 3.04 (25)	1.18 ± 3.31 (11)
	Difference from placebo [95% CI][a)]	−0.42 [−1.23 ,0.39]	0.20 [−0.61, 1.01]			0.40 [−1.42, 2.22]	0.54 [−0.91, 2.00]		1.45 [−0.31, 3.21]
	Subjects with mTSS ≤0 (NRI)	68.3 (28/41)	67.5 (27/40)	64.3 (18/28)	55.3 (21/38)	72.7 (8/11)	65.2 (15/23)	76.0 (19/25)	75.0 (9/12)
Week 52	Entire study population								
	Change from baseline in mTSS	0.50 ± 2.10 (411)	0.21 ± 1.43 (417)	0.58 ± 3.62 (273)		0.23 ± 1.11 (176)	0.31 ± 1.81 (345)	0.81 ± 3.09 (330)	0.33 ± 1.90 (166)
	Subjects with mTSS ≤0 (NRI)	69.6 (334/480)	76.8 (365/475)	69.2 (225/325)		64.7 (134/207)	66.8 (278/416)	56.0 (233/416)	61.0 (128/210)
	Japanese subpopulation								
	Change from baseline in mTSS	1.19 ± 3.92 (40)	0.31 ± 2.01 (40)	0.67 ± 1.49 (26)		0.76 ± 2.86 (10)	0.29 ± 2.80 (22)	0.50 ± 0.96 (22)	1.55 ± 3.29 (10)
	Subjects with mTSS ≤0 (NRI)	75.6 (31/41)	75.0 (30/40)	67.9 (19/28)		63.6 (7/11)	78.3 (18/23)	60.0 (15/25)	66.7 (8/12)

Change from baseline in mTSS, mean ± standard deviation (N); subjects with mTSS ≤0, % (n/N); ADA, adalimumab; *, primary endpoint
Week 52 data include data of subjects who received standard of care for RA.
a) An MMRM model using treatment, visit, treatment by visit interaction, geographical region, prior use of biologics, result (positive vs. negative) for anti-CCP antibodies or RF at screening, and baseline values as covariates, assuming an unstructured covariance structure between timepoints. (For the Japanese subpopulation analysis, geographical region, prior use of biologics, and result [positive vs. negative] for anti-CCP antibodies or RF at screening were not included in the modeling. In the FINCH3 study, prior use of biologics was not used as the stratification factor in the modeling.)

In the FINCH1 study, statistically significant differences versus placebo in the change from baseline in mTSS at Week 24, the primary endpoint, were observed in the 100 mg and 200 mg groups, demonstrating the

superiority of filgotinib 100 mg and 200 mg over placebo [see Section 7.1.1]. At 100 mg, the results of the Japanese subpopulation tended to be similar to those of the entire study population while at 200 mg, the change from baseline in mTSS is greater than that of placebo in the Japanese subpopulation, a trend different from that of the entire study population. This may be attributable to factors including the limited number of Japanese subjects and mTSS being an endpoint with high variability; however, given the discussion on the proportion of subjects who had radiographic evidence of no structural damage progression as summarized below, filgotinib is expected to have efficacy in reducing structural damage to the joint in Japanese patients with RA who had an inadequate response to conventional therapies.

- Both in the entire study population and Japanese subpopulation, the proportion of subjects who had radiographic evidence of no structural damage progression (mTSS ≤0) at Week 24 tends to be higher in the 100 mg and 200 mg groups than in the placebo group.
- The study included an active comparator of adalimumab, which was demonstrated to inhibit structural damage to the joint. In both the entire study population and Japanese subpopulation, the proportion of subjects who had radiographic evidence of no structural damage progression (mTSS ≤0) at Week 24 in the filgotinib groups was similar to that of the adalimumab group. Additionally, in both populations, the change from baseline in mTSS and the proportion of subjects who had radiographic evidence of no structural damage progression (mTSS ≤0) at Week 52 in the filgotinib groups were similar to those of the adalimumab group.

In the FINCH3 study, there were no statistically significant differences in the change from baseline in mTSS at Week 24, the primary endpoint, in any of the filgotinib groups compared to the placebo group [see Section 7.1.3]. In the Japanese subpopulation, the change from baseline in mTSS was greater in the filgotinib groups than in the placebo group, a trend different from that of the entire study population. However, given that clinical remission as defined by CDAI criteria has been suggested to be well correlated with mTSS (*Ann Rheum Dis.* 2015;74:1676-83, *Rheumatol Ther.* 2018;5:341-53) in addition to the results at Week 52 and the proportion of subjects who had radiographic evidence of no structural damage progression, long-term treatment with filgotinib is likely to inhibit structural damage to the joint in MTX-naïve patients with RA [for data of CDAI remission, see Table 57 and Table 59].

PMDA's view:

In the FINCH3 study, which was conducted in MTX-naïve patients with RA, the primary endpoint, the difference in the change from baseline in mTSS at Week 24 from placebo, was not statistically significant in any of the filgotinib groups. In the FINCH1 study, which was conducted in patients with RA who had an inadequate response to MTX, the difference from placebo was statistically significant for the same endpoint in any of the filgotinib groups, which demonstrates the efficacy of filgotinib in reducing structural damage to the joint in patients with RA who had an inadequate response to conventional therapies, a patient population eligible for treatment with filgotinib, which will be discussed later [for indication and clinical positioning, see Section 7.R.4].

In the FINCH1 study, some results in the Japanese subpopulation differ from those of the entire study population. However, PMDA concluded that filgotinib is expected to have efficacy in inhibiting structural damage to the joint in Japanese patients with RA similarly in the entire study population based on the following: the disagreement is due to limited number of Japanese subjects as well as mTSS a measure known to produce high variability, thus making the results easily affected by data of a few subjects who showed a major change from baseline; results of the proportion of subjects who had radiographic evidence of no structural damage progression (mTSS ≤0) at Week 24 and at Week 52, and the change from baseline in mTSS at Week 52 support that filgotinib is effective in inhibiting structural damage to the joint.

The above conclusion by PMDA will be further discussed at the Expert Discussion.

7.R.3 Safety

7.R.3.1 Summary of safety

The applicant's explanation about the safety of filgotinib based on the results of pooled data analysis of the following studies (pooled population from the 7 phase II/III studies) and other findings: 3 foreign phase II studies in Japanese and non-Japanese patients with RA (Studies GLPG0634-CL-203, GLPG0634-CL-204, and GLPG0634-CL-205) and 4 global phase III studies (the FINCH1, FINCH2, FINCH3, and FINCH4 studies [data cut-off in September 2019]).

Table 61 summarizes the safety data of the pooled population from the 7 phase II/III studies.

Table 61. Summary of safety data from clinical studies in patients with RA (pooled population from the 7 phase II/III studies)

	Up to Week 12				Overall treatment period			
	100 mg	200 mg	Adalimumab	Placebo/MTX	100 mg	200 mg	Adalimumab	Placebo/MTX
Entire study population								
N	1,647	2,267	325	1,197	1,647	2,267	325	1,197
Duration of total exposure (patient-years)	375.7	515.6	74.3	268.1	2,032.9	4,047.7	290.1	658.5
All adverse events	643 (39.0) 171.1	910 (40.1) 176.5	131 (40.3) 176.3	521 (43.5) 194.3	1,140 (69.2) 56.1	1,771 (78.1) 43.8	239 (73.5) 82.4	731 (61.1) 111.0
Serious adverse events	35 (2.1) 9.3	53 (2.3) 10.3	9 (2.8) 12.1	21 (1.8) 7.8	166 (10.1) 8.2	254 (11.2) 6.3	22 (6.8) 7.6	59 (4.9) 9.0
Adverse events leading to study drug discontinuation	22 (1.3) 5.9	36 (1.6) 7.0	10 (3.1) 13.5	20 (1.7) 7.5	93 (5.6) 4.6	239 (10.5) 5.9	18 (5.5) 6.2	47 (3.9) 7.1
Adverse reactions	242 (14.7) 64.4	339 (15.0) 65.8	44 (13.5) 59.2	205 (17.1) 76.5	478 (29.0) 23.5	826 (36.4) 20.4	91 (28.0) 31.4	301 (25.1) 45.7
Deaths	1 (<0.1) 0.3	3 (0.1) 0.6	0 0	1 (<0.1) 0.4	6 (0.4) 0.3	19 (0.8) 0.5	1 (0.3) 0.3	2 (0.2) 0.3
Japanese subpopulation								
N	107	124	28	76	107	124	28	76
Duration of total exposure (patient-years)	24.7	28.4	6.4	16.9	140.3	171.2	23.0	40.4
All adverse events	55 (51.4) 222.8	75 (60.5) 263.8	16 (57.1) 248.4	49 (64.5) 289.9	89 (83.2) 63.4	117 (94.4) 68.4	26 (92.9) 113.1	58 (76.3) 143.5
Serious adverse events	2 (1.9) 8.1	3 (2.4) 10.6	2 (7.1) 31.1	2 (2.6) 11.8	12 (11.2) 8.6	17 (13.7) 9.9	3 (10.7) 13.1	6 (7.9) 14.8
Adverse events leading to study drug discontinuation	0 0	4 (3.2) 14.1	2 (7.1) 31.1	4 (5.3) 23.7	5 (4.7) 3.6	13 (10.5) 7.6	3 (10.7) 13.1	7 (9.2) 17.3
Adverse reactions	27 (25.2) 109.4	36 (29.0) 126.6	7 (25.0) 108.7	32 (42.1) 189.3	58 (54.2) 41.3	76 (61.3) 44.4	11 (39.3) 47.9	35 (46.1) 86.6
Deaths	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Upper row, n (%); lower row, number of events per 100 person-years (PY) adjusted by duration of total exposure

During the overall treatment period, among subjects who received filgotinib, death occurred in 6 subjects at 100 mg (varicella, malignant peritoneal neoplasm/ovarian cancer, cardiac arrest, cardiopulmonary failure, myocardial infarction, and vertebral artery aneurysm/intracranial aneurysm) and 19 subjects at 200 mg (non-Hodgkin's lymphoma in 2 subjects,[34)] pneumonia/septic shock in 2 subjects, pneumonia,[26)] ischaemic stroke [2 events]/deep vein thrombosis/pulmonary embolism, cardiac failure, ischaemic stroke, lung adenocarcinoma, acute myocardial infarction, cerebrovascular accident, alveolitis/bronchiectasis/bronchitis/pulmonary fibrosis/respiratory failure/rheumatoid lung/cor pulmonale chronic, staphylococcal sepsis, death,[26)] pneumonia/septic shock/acute kidney injury/electrolyte imbalance, interstitial lung disease, oesophageal squamous cell carcinoma metastatic, lupus myocarditis, and pericarditis). Among these events, a causal relationship to the study drug could not be ruled out for 1 subject at 100 mg (varicella) and 11 subjects at 200 mg (non-Hodgkin's lymphoma in 2 subjects, pneumonia in 2 subjects, pneumonia/septic shock in 2 subjects, deep vein thrombosis/pulmonary embolism, acute myocardial infarction, staphylococcal sepsis, interstitial lung disease, and oesophageal squamous cell carcinoma metastatic). No deaths occurred in Japanese subjects.[35)]

[34)] Because non-Hodgkin's lymphoma occurred in 1 subject ≥30 days after administration of the last dose of the study drug, it was not classified as a treatment-emergent adverse event.

[35)] In the FINCH4 study, sudden death occurred in 1 Japanese subject receiving the 100 mg dose on [redacted], which was after the data cut-off date. A causal relationship to the study drug could not be ruled out.

The above results showed that the incidence of adverse events (including serious adverse events and adverse events leading to study drug discontinuation), incidence of adverse reactions, and incidence of deaths were similar across all treatment groups in the pooled population from the 7 phase II/III studies (up to Week 12). In the analysis of the overall treatment period for the pooled population from the 7 phase II/III studies, the incidence of the abovementioned adverse events, adverse reactions, and deaths was higher in the filgotinib groups than in other groups; however, there were no clear differences in the exposure-adjusted incidence rate between the treatment groups. No clear dose-dependent relationship was observed in the safety profiles of filgotinib.

The incidences of all adverse events and adverse reactions, as well as the exposure-adjusted incidence rate in the Japanese subpopulation were higher than those of the entire study population; however, there were no clear differences between the treatment groups. Therefore, the major reason for the difference was considered to be caused by high incidence of adverse events classified as System Organ Class (SOC) "infections and infestations" in the Japanese subpopulation compared with the entire study population [see Section 7.R.3.2]. There were no clear differences between the entire study population and Japanese subpopulation in other respects.

Table 62 shows major adverse events in the pooled population from the 7 phase II/III studies.

Table 62. Adverse events occurring in ≥5% of subjects in any group (pooled population from the 7 phase II/III studies, overall treatment period)

Adverse events	Entire study population				Japanese subpopulation			
	100 mg (N = 1,647)	200 mg (N = 2,267)	Adalimumab (N = 325)	Placebo/MTX (N = 1,197)	100 mg (N = 107)	200 mg (N = 124)	Adalimumab (N = 28)	Placebo/MTX (N = 76)
Upper respiratory tract infection	127 (7.7)	224 (9.9)	21 (6.5)	57 (4.8)	8 (7.5)	7 (5.6)	1 (3.6)	2 (2.6)
Nasopharyngitis	135 (8.2)	212 (9.4)	24 (7.4)	61 (5.1)	25 (23.4)	46 (37.1)	3 (10.7)	16 (21.1)
Urinary tract infection	97 (5.9)	164 (7.2)	17 (5.2)	23 (1.9)	1 (0.9)	0	0	1 (1.3)
Nausea	80 (4.9)	150 (6.6)	6 (1.8)	68 (5.7)	11 (10.3)	14 (11.3)	1 (3.6)	5 (6.6)
Hypertension	73 (4.4)	136 (6.0)	15 (4.6)	26 (2.2)	1 (0.9)	3 (2.4)	0	2 (2.6)
Bronchitis	69 (4.2)	132 (5.8)	10 (3.1)	40 (3.3)	4 (3.7)	7 (5.6)	0	7 (9.2)
Headache	65 (3.9)	119 (5.2)	13 (4.0)	49 (4.1)	5 (4.7)	10 (8.1)	1 (3.6)	5 (6.6)
Rheumatoid arthritis	91 (5.5)	102 (4.5)	11 (3.4)	48 (4.0)	15 (14.0)	11 (8.9)	4 (14.3)	8 (10.5)
Diarrhoea	44 (2.7)	83 (3.7)	10 (3.1)	36 (3.0)	5 (4.7)	7 (5.6)	0	2 (2.6)
ALT increased	49 (3.0)	81 (3.6)	22 (6.8)	22 (1.8)	6 (5.6)	0	0	0
Back pain	44 (2.7)	79 (3.5)	7 (2.2)	27 (2.3)	5 (4.7)	8 (6.5)	2 (7.1)	2 (2.6)
Arthralgia	52 (3.2)	75 (3.3)	7 (2.2)	19 (1.6)	3 (2.8)	4 (3.2)	2 (7.1)	0
Influenza	39 (2.4)	74 (3.3)	6 (1.8)	21 (1.8)	7 (6.5)	14 (11.3)	3 (10.7)	1 (1.3)
Pharyngitis	28 (1.7)	72 (3.2)	6 (1.8)	21 (1.8)	3 (2.8)	8 (6.5)	1 (3.6)	3 (3.9)
Hypercholesterolaemia	30 (1.8)	68 (3.0)	4 (1.2)	7 (0.6)	3 (2.8)	1 (0.8)	2 (7.1)	0
AST increased	38 (2.3)	66 (2.9)	18 (5.5)	16 (1.3)	4 (3.7)	0	0	0
Abdominal pain upper	26 (1.6)	59 (2.6)	7 (2.2)	13 (1.1)	2 (1.9)	6 (4.8)	2 (7.1)	0
Dyslipidaemia	26 (1.6)	58 (2.6)	2 (0.6)	8 (0.7)	5 (4.7)	5 (4.0)	2 (7.1)	1 (1.3)
Vomiting	31 (1.9)	52 (2.3)	6 (1.8)	19 (1.6)	2 (1.9)	6 (4.8)	2 (7.1)	0
Dizziness	25 (1.5)	52 (2.3)	2 (0.6)	13 (1.1)	4 (3.7)	7 (5.6)	0	0
Fall	23 (1.4)	38 (1.7)	2 (0.6)	6 (0.5)	4 (3.7)	10 (8.1)	1 (3.6)	0
Contusion	17 (1.0)	38 (1.7)	4 (1.2)	11 (0.9)	4 (3.7)	6 (4.8)	0	4 (5.3)
Abdominal discomfort	14 (0.9)	29 (1.3)	2 (0.6)	10 (0.8)	4 (3.7)	9 (7.3)	1 (3.6)	4 (5.3)
Hepatic enzyme increased	12 (0.7)	22 (1.0)	6 (1.8)	4 (0.3)	0	7 (5.6)	0	0
Stomatitis	15 (0.9)	16 (0.7)	1 (0.3)	13 (1.1)	9 (8.4)	6 (4.8)	0	8 (10.5)
Dental caries	10 (0.6)	16 (0.7)	1 (0.3)	3 (0.3)	7 (6.5)	6 (4.8)	1 (3.6)	1 (1.3)
Hepatic function abnormal	6 (0.4)	13 (0.6)	0	7 (0.6)	4 (3.7)	8 (6.5)	0	3 (3.9)
Eczema	7 (0.4)	12 (0.5)	3 (0.9)	11 (0.9)	1 (0.9)	5 (4.0)	1 (3.6)	6 (7.9)
Pruritus	8 (0.5)	7 (0.3)	6 (1.8)	6 (0.5)	1 (0.9)	2 (1.6)	2 (7.1)	0
Dry skin	2 (0.1)	3 (0.1)	2 (0.6)	2 (0.2)	0	0	2 (7.1)	0

n (%)

Major serious adverse events and adverse events leading to study drug discontinuation in the pooled population from the 7 phase II/III studies are shown in Table 63 and Table 64, respectively.

Table 631. Serious adverse events occurring in ≥3 subjects in any group (pooled population from the 7 phase II/III studies, overall treatment period)

Adverse events	100 mg (N = 1,647)	200 mg (N = 2,267)	Adalimumab (N = 325)	Placebo/MTX (N = 1,197)
Pneumonia	10 (0.6)	18 (0.8)	3 (0.9)	2 (0.2)
Osteoarthritis	9 (0.5)	7 (0.3)	0	1 (<0.1)
Acute kidney injury	2 (0.1)	7 (0.3)	0	0
Acute respiratory failure	1 (<0.1)	7 (0.3)	0	0
Pulmonary embolism	1 (<0.1)	6 (0.3)	0	2 (0.2)
Atrial fibrillation	1 (<0.1)	5 (0.2)	0	1 (<0.1)
Cholelithiasis	1 (<0.1)	5 (0.2)	0	0
Cellulitis	4 (0.2)	4 (0.2)	1 (0.3)	0
Anaemia	4 (0.2)	4 (0.2)	0	0
Acute myocardial infarction	2 (0.1)	4 (0.2)	1 (0.3)	1 (<0.1)
Coronary artery disease	2 (0.1)	4 (0.2)	0	0
Cataract	1 (<0.1)	4 (0.2)	1 (0.3)	1 (<0.1)
Femur fracture	1 (<0.1)	4 (0.2)	0	2 (0.2)
Nephrolithiasis	4 (0.2)	3 (0.1)	0	1 (<0.1)
Bronchitis	3 (0.2)	3 (0.1)	0	2 (0.2)
Herpes zoster	1 (<0.1)	3 (0.1)	0	0
Sepsis	0	3 (0.1)	1 (0.3)	1 (<0.1)
Cholecystitis acute	0	3 (0.1)	0	0
Rheumatoid arthritis	4 (0.2)	2 (<0.1)	0	3 (0.3)
Pyelonephritis acute	4 (0.2)	2 (<0.1)	0	0
Dyspnoea	3 (0.2)	1 (<0.1)	0	1 (<0.1)
Inguinal hernia	3 (0.2)	1 (<0.1)	0	0
Appendicitis	4 (0.2)	0	0	2 (0.2)
Transient ischaemic attack	3 (0.2)	0	0	0

n (%)

Table 64. Adverse events leading to study drug discontinuation in ≥0.5% of subjects in any group (pooled population from the 7 phase II/III studies, overall treatment period)

Adverse events	100 mg (N = 1,647)	200 mg (N = 2,267)	Adalimumab (N = 325)	Placebo/MTX (N = 1,197)
Mycobacterium tuberculosis complex test positive	8 (0.5)	48 (2.1)	0	0
Pneumonia	5 (0.3)	15 (0.7)	2 (0.6)	2 (0.2)
Blood creatinine increased	0	12 (0.5)	0	0
Lymphopenia	2 (0.1)	11 (0.5)	0	0
ALT increased	1 (<0.1)	4 (0.2)	2 (0.6)	1 (<0.1)
AST increased	1 (<0.1)	3 (0.1)	2 (0.6)	1 (<0.1)
Rheumatoid arthritis	3 (0.2)	0	2 (0.6)	6 (0.5)

n (%)

Adverse events of special interest will be discussed in Section 7.R.3.2 below.

7.R.3.2 Adverse events associated with filgotinib treatment

PMDA's safety evaluation primarily focused on adverse events of interest that are likely to be associated with filgotinib treatment based on the incidence of adverse events reported in the clinical studies, the pharmacological action of filgotinib, and other factors. The data for adverse events of interest in the pooled population from the 7 phase II/III studies are summarized in Table 65 (up to Week 12) and Table 66 (overall treatment period).

Table 65. Summary of adverse events of interest (pooled population from the 7 phase II/III studies, up to Week 12)

	Entire study population				Japanese subpopulation			
	100 mg	200 mg	Adalimumab	Placebo/MTX	100 mg	200 mg	Adalimumab	Placebo/MTX
N	1,647	2,267	325	1,197	107	124	28	76
Duration of total exposure (patient-years)	375.7	515.6	74.3	268.1	24.7	28.4	6.4	16.9
Infections[a)]	241 (14.6) 64.1	337 (14.9) 65.4	60 (18.5) 80.7	169 (14.1) 63.0	18 (16.8) 72.9	35 (28.2) 123.1	6 (21.4) 93.2	17 (22.4) 100.6
Serious infections[b)]	9 (0.5) 2.4	12 (0.5) 2.3	5 (1.5) 6.7	6 (0.5) 2.2	0 0	2 (1.6) 7.0	2 (7.1) 31.1	1 (1.3) 5.9
Opportunistic infections[c)]	0 0	0 0	1 (0.3) 1.3	0 0	0 0	0 0	1 (3.6) 15.5	0 0
Active tuberculosis[c)]	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Latent tuberculosis[c)]	11 (0.7) 2.9	9 (0.4) 1.7	0 0	0 0	1 (0.9) 4.1	0 0	0 0	0 0
Pneumocystis pneumonia[d)]	0 0	0 0	1 (0.3) 1.3	0 0	0 0	0 0	1 (3.6) 15.5	0 0
Herpes zoster[c)]	4 (0.2) 1.1	7 (0.3) 1.4	0 0	4 (0.3) 1.5	0 0	0 0	0 0	0 0
Viral reactivation[e)]	0 0	2 (<0.1) 0.4	1 (0.3) 1.3	1 (<0.1) 0.4	0 0	0 0	0 0	0 0
Malignancy (excluding NMSC)[c)]	1 (<0.1) 0.3	0 0	1 (0.3) 1.3	2 (0.2) 0.7	0 0	0 0	1 (3.6) 15.5	0 0
NMSC[c)]	0 0	1 (<0.1) 0.2	0 0	0 0	0 0	0 0	0 0	0 0
Gastrointestinal perforation[c)]	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Interstitial lung disease (SMQ/narrow search)	0 0	0 0	0 0	1 (<0.1) 0.4	0 0	0 0	0 0	1 (1.3) 5.9
Dyslipidaemia[c)]	27 (1.6) 7.2	44 (1.9) 8.5	5 (1.5) 6.7	14 (1.2) 5.2	1 (0.9) 4.1	7 (5.6) 24.6	3 (10.7) 46.6	0 0
MACE[f)]	4 (0.2) 1.1	3 (0.1) 0.6	0 0	2 (0.2) 0.7	0 0	0 0	0 0	0 0
Venous thromboembolism event[g)]	0 0	1 (<0.1) 0.2	0 0	0 0	0 0	0 0	0 0	0 0
Haemoglobin decreased or anaemia[c)]	19 (1.2) 5.1	17 (0.7) 3.3	5 (1.5) 6.7	23 (1.9) 8.6	2 (1.9) 8.1	1 (0.8) 3.5	0 0	1 (1.3) 5.9
Neutrophil count decreased or neutropenia[c)]	11 (0.7) 2.9	11 (0.5) 2.1	4 (1.2) 5.4	2 (0.2) 0.7	0 0	1 (0.8) 3.5	0 0	0 0
Lymphocyte count decreased or lymphopenia[c)]	14 (0.9) 3.7	14 (0.6) 2.7	0 0	9 (0.8) 3.4	1 (0.9) 4.1	2 (1.6) 7.0	0 0	1 (1.3) 5.9
Platelet count decreased or thrombocytopenia[c)]	1 (<0.1) 0.3	5 (0.2) 1.0	0 0	2 (0.2) 0.7	0 0	1 (0.8) 3.5	0 0	0 0
CPK increased or muscle disorder[c)]	2 (0.1) 0.5	14 (0.6) 2.7	1 (0.3) 1.3	1 (<0.1) 0.4	0 0	3 (2.4) 10.6	0 0	0 0
Rhabdomyolysis (PT)	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Myopathy[h)]	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Liver disorder[i)]	36 (2.2) 9.6	59 (2.6) 11.4	9 (2.8) 12.1	30 (2.5) 11.2	6 (5.6) 24.3	6 (4.8) 21.1	0 0	4 (5.3) 23.7
Renal disorder[c)]	12 (0.7) 3.2	11 (0.5) 2.1	0 0	8 (0.7) 3.0	3 (2.8) 12.2	0 0	0 0	0 0
Hypophosphataemia[j)]	1 (<0.1) 0.3	1 (<0.1) 0.2	0 0	2 (0.2) 0.7	0 0	0 0	0 0	0 0

Upper row, n (%); lower row, number of events per 100 person-years (PY) adjusted by duration of total exposure
For notes, see the footnotes of Table 66.

Table 66. Summary of adverse events of interest (pooled population from the 7 phase II/III studies, overall treatment period)

	Entire study population				Japanese subpopulation			
	100 mg	200 mg	Adalimumab	Placebo/MTX	100 mg	200 mg	Adalimumab	Placebo/MTX
N	1,647	2,267	325	1,197	107	124	28	76
Duration of total exposure (patient-years)	2,032.9	4,047.7	290.1	658.5	140.3	171.2	23.0	40.4
Infections[a)]	648 (39.3) 31.9	1,074 (47.4) 26.5	129 (39.7) 44.5	324 (27.1) 49.2	54 (50.5) 38.5	81 (65.3) 47.3	13 (46.4) 56.6	30 (39.5) 74.2
Serious infections[b)]	51 (3.1) 2.5	67 (3.0) 1.7	10 (3.1) 3.4	15 (1.3) 2.3	3 (2.8) 2.1	7 (5.6) 4.1	3 (10.7) 13.1	3 (3.9) 7.4
Opportunistic infections[c)]	4 (0.2) 0.2	5 (0.2) 0.1	2 (0.6) 0.7	2 (0.2) 0.3	0 0	2 (1.6) 1.2	1 (3.6) 4.4	1 (1.3) 2.5
Active tuberculosis[c)]	3 (0.2) 0.1	0 0	1 (0.3%) 0.3	0 0	0 0	0 0	0 0	0 0
Latent tuberculosis[c)]	55 (3.3) 2.7	129 (5.7) 3.2	1 (0.3) 0.3	1 (<0.1) 0.2	2 (1.9) 1.4	0 0	0 0	0 0
Pneumocystis pneumonia[d)]	0 0	0 0	1 (0.3) 0.3	1 (<0.1) 0.2	0 0	0 0	1 (3.6) 4.4	1 (1.3) 2.5
Herpes zoster[c)]	23 (1.4) 1.1	74 (3.3) 1.8	2 (0.6) 0.7	7 (0.6) 1.1	3 (2.8) 2.1	5 (4.0) 2.9	0 0	0 0
Viral reactivation[e)]	5 (0.3) 0.2	8 (0.4) 0.2	2 (0.6) 0.7	1 (<0.1) 0.2	0 0	1 (0.8) 0.6	0 0	0 0
Malignancy (excluding NMSC[c)])	11 (0.7) 0.5	22 (1.0) 0.5	2 (0.6) 0.7	7 (0.6) 1.1	1 (0.9) 0.7	2 (1.6) 1.2	1 (3.6) 4.4	1 (1.3) 2.5
NMSC[c)]	3 (0.2) 0.1	9 (0.4) 0.2	0 0	1 (<0.1) 0.2	0 0	0 0	0 0	0 0
Gastrointestinal perforation[c)]	0 0	3 (0.1) 0.1	0 0	0 0	0 0	1 (0.8) 0.6	0 0	0 0
Interstitial lung disease (SMQ/narrow search)	6 (0.4) 0.3	13 (0.6) 0.3	0 0	2 (0.2) 0.3	0 0	0 0	0 0	1 (1.3) 2.5
Dyslipidaemia[c)]	84 (5.1) 4.1	206 (9.1) 5.1	9 (2.8) 3.1	28 (2.3) 4.3	10 (9.3) 7.1	12 (9.7) 7.0	4 (14.3) 17.4	1 (1.3) 2.5
MACE[f)]	13 (0.8) 0.6	19 (0.8) 0.5	1 (0.3) 0.3	5 (0.4) 0.8	0 0	1 (0.8) 0.6	0 0	0 0
Venous thromboembolism event[g)]	1 (<0.1) 0.0	8 (0.4) 0.2	1 (0.3) 0.3	4 (0.3) 0.6	0 0	1 (0.8) 0.6	0 0	1 (1.3) 2.5
Haemoglobin decreased or anaemia[c)]	63 (3.8) 3.1	89 (3.9) 2.2	12 (3.7) 4.1	37 (3.1) 5.6	2 (1.9) 1.4	5 (4.0) 2.9	0 0	2 (2.6) 4.9
Neutrophil count decreased or neutropenia[c)]	24 (1.5) 1.2	36 (1.6) 0.9	7 (2.2) 2.4	5 (0.4) 0.8	1 (0.9) 0.7	2 (1.6) 1.2	1 (3.6) 4.4	0 0
Lymphocyte count decreased or lymphopenia[c)]	34 (2.1) 1.7	87 (3.8) 2.1	3 (0.9) 1.0	14 (1.2) 2.1	3 (2.8) 2.1	5 (4.0) 2.9	0 0	1 (1.3) 2.5
Platelet count decreased or thrombocytopenia[c)]	5 (0.3) 0.2	14 (0.6) 0.3	2 (0.6) 0.7	5 (0.4) 0.8	0 0	1 (0.8) 0.6	0 0	0 0
CPK increased or muscle disorders[c)]	15 (0.9) 0.7	40 (1.8) 1.0	2 (0.6) 0.7	4 (0.3) 0.6	0 0	4 (3.2) 2.3	0 0	0 0
Rhabdomyolysis (PT)	0 0	1 (<0.1) 0.0	0 0	0 0	0 0	0 0	0 0	0 0
Myopathy[h)]	0 0	1 (<0.1) 0.0	0 0	0 0	0 0	0 0	0 0	0 0
Liver disorder[i)]	113 (6.9) 5.6	219 (9.7) 5.4	33 (10.2) 11.4	57 (4.8) 8.7	17 (15.9) 12.1	27 (21.8) 15.8	0 0	6 (7.9) 14.8
Renal disorder[c)]	31 (1.9) 1.5	72 (3.2) 1.8	1 (0.3) 0.3	12 (1.0) 1.8	5 (4.7) 3.6	4 (3.2) 2.3	0 0	0 0
Hypophosphataemia[j)]	2 (0.1) 0.1	6 (0.3) 0.1	2 (0.6) 0.7	3 (0.3) 0.5	0 0	0 0	0 0	0 0

Upper row, n (%); lower row, number of events per 100 person-years (PY) adjusted by duration of total exposure

a) Infections and infestations (SOC); b) serious adverse events classified into infections and infestations (SOC); c) events are based on the MedDRA queries prepared by the applicant;

d) Preferred terms (PTs) pneumocystis jirovecii pneumonia and pneumocystis jirovecii infection;

e) Events that include the following PTs except herpes zoster: adenovirus infection, cytomegalovirus infection, Epstein-Barr (EB) virus infection, herpes simplex, human herpesvirus (HHV)-6 infection, HHV-7 infection, parvovirus B19 infection, BK virus infection, JC virus infection, infection reactivation;

f) Events adjudicated by an independent committee: cardiovascular death (death due to acute myocardial infarction, sudden cardiac death, death due to cardiac failure, stroke, cardiovascular treatment, cardiovascular haemorrhage, and other cardiovascular causes), myocardial infarction (presence of myocardial necrosis, supported by the evidence, in the clinical setting of myocardial ischaemia), and stroke;

g) Events adjudicated by an independent committee: deep vein thrombosis/pulmonary embolism-related systemic arterial thromboembolism and venous thrombosis;

h) Rhabdomyolysis/myopathy (SMQ/narrow search); i) Drug related hepatic disorders (SMQ/comprehensive search);

j) Events that include the following PTs: blood phosphorus decreased, hypophosphataemia, hypophosphataemic osteomalacia, and urine phosphorus increased

(a) Infections

1) Infections and serious infections

The applicant's explanation about the incidence of infections:

Infections and serious infections that occurred in the pooled population from the 7 phase II/III studies are summarized in Table 65 (up to Week 12) and Table 66 (overall treatment period).

In the entire study population, the incidences and exposure-adjusted incidence rates of infections and serious infections in the filgotinib groups were similar to those in the placebo/MTX group and to the adalimumab group. No clear dose-dependency was observed in the filgotinib groups. Major events of infections were upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis, while major serious infections were pneumonia, bronchitis, and cellulitis.

While the incidences and exposure-adjusted incidence rates of infections and serious infections in the Japanese subpopulation were higher than the entire study population, there were no clear differences between the placebo/MTX-treated subjects and filgotinib groups within the Japanese subpopulation. Events reported in the Japanese subpopulation were similar to those in the entire study population. The incidences of influenza and herpes zoster tended to increase in filgotinib-treated subjects compared with those in the placebo/MTX-treated subjects and adalimumab-treated subjects (the exposure-adjusted incidence rate of influenza: 5.0 events/100 person-years (PY) in the 100 mg-treated subjects, 8.8 events/100 PY in the 200 mg-treated subjects, 13.1 events/100 PY in the adalimumab-treated subjects, and 2.5 events/100 PY in the placebo/MTX-treated subjects; for the herpes zoster data, see Table 66).

Although there are limitations in comparing the studies, the exposure-adjusted incidence rate of serious infections in filgotinib-treated subjects in the pooled population from the 7 phase II/III studies (overall treatment period) was similar to the incidence rates reported in long-term studies of the previously approved JAK inhibitors in patients with RA: 2.4 events/100 PY for tofacitinib (*Arthritis Res Ther*. 2019;21:89) and 2.9 events/100 PY for baricitinib (*J Rheumatol.* 2019;46:7-18).

Table 67 shows the incidences of infections and serious infections by subgroup defined by key patient characteristics. In any subgroup, exposure-adjusted incidence rates showed no consistent trends.

Table 67. Incidences of infections and serious infections by subgroup defined by patient characteristics (pooled population from the 7 phase II/III studies, overall treatment period)

Adverse events		Infections				Serious infections			
Treated Subjects		100 mg	200 mg	Adalimumab	Placebo/MTX	100 mg	200 mg	Adalimumab	Placebo/MTX
N		1,647	2,267	325	1,197	1,647	2,267	325	1,197
Duration of total exposure (patient-years)		2,032.9	4,047.7	290.1	658.5	2,032.9	4,047.7	290.1	658.5
Entire study population		39.3 (648/1,647) 31.9	47.4 (1074/2,267) 26.5	39.7 (129/325) 44.5	27.1 (324/1,197) 49.2	3.1 (51/1,647) 2.5	3.0 (67/2,267) 1.7	3.1 (10 /325) 3.4	1.3 (15/1,197) 2.3
Age	<65 years	39.3 (519/1,320) 32.2	46.4 (861/1,857) 25.4	38.8 (100/258) 43.1	27.0 (257/952) 49.3	3.0 (40/1,320) 2.5	2.7 (50/1,857) 1.5	2.3 (6/258) 2.6	1.1 (10/952) 1.9
	≥65 years	39.4 (129/327) 30.5	52.0 (213/410) 32.5	43.3 (29/67) 49.8	27.3 (67/245) 48.8	3.4 (11/327) 2.6	4.1 (17/410) 2.6	6.0 (4/67) 6.9	2.0 (5/245) 3.6
Body weight	<60 kg	45.2 (176/389) 37.1	47.7 (268/562) 27.7	42.0 (37/88) 48.3	26.8 (81/302) 50.4	4.9 (19/389) 4.0	2.5 (14/562) 1.4	3.4 (3/88) 3.9	2.0 (6/302) 3.7
	≥60 kg <100 kg	36.4 (406/1,115) 29.7	46.1 (696/1,509) 25.4	38.4 (81/211) 41.8	25.5 (201/787) 46.2	2.2 (24/1,115) 1.8	3.0 (46/1,509) 1.7	2.8 (6/211) 3.1	1.1 (9/787) 2.1
	≥100 kg	46.2 (66/143) 34.4	56.1 (110/196) 32.5	42.3 (11/26) 55.3	38.9 (42/108) 66.7	5.6 (8/143) 4.2	3.6 (7/196) 2.1	3.8 (1/26) 5.0	0 (0/108) 0
Anti-rheumatic drug	None	17.0 (25/147) 37.7	46.9 (199/424) 19.9	0 (0/0) 0	10.1 (7/69) 45.4	2.0 (3/147) 4.5	4.5 (19/424) 1.9	0 (0/0) 0	0 (0/69) 0
	MTX alone	41.0 (534/1,302) 31.2	46.9 (755/1,610) 27.9	38.2 (109/285) 42.7	28.9 (282/977) 50.0	3.1 (41/1,302) 2.4	2.5 (40/1,610) 1.5	3.2 (9/285) 3.5	1.4 (14/977) 2.5
	Non-MTX cDMARDs	52.4 (22/42) 45.6	58.3 (35/60) 35.8	0 (0/0) 0	11.8 (4/34) 32.0	11.9 (5/42) 10.4	5.0 (3/60) 3.1	0 (0/0) 0	0 (0/34) 0
	MTX + cDMARDs	42.9 (67/156) 32.3	49.1 (85/173) 35.2	50.0 (20/40) 57.3	26.5 (31/117) 46.2	1.3 (2/156) 1.0	2.9 (5/173) 2.1	2.5 (1/40) 2.9	0.9 (1/117) 1.5
Concurrent corticosteroid	No	36.6 (372/1,016) 32.2	47.3 (703/1,486) 23.9	42.2 (78/185) 47.0	26.6 (193/726) 49.8	2.6 (26/1,016) 2.2	2.8 (41/1,486) 1.4	3.2 (6/185) 3.6	1.0 (7/726) 1.8
	Yes	43.7 (276/631) 31.5	47.5 (371/781) 33.5	36.4 (51/140) 41.1	27.8 (131/471) 48.3	4.0 (25/631) 2.9	3.3 (26/781) 2.3	2.9 (4/140) 3.2	1.7 (8/471) 2.9

Upper and middle rows, % (n/N of the subgroup); lower row, number of events per 100 person-years (PY) adjusted by duration of total exposure

Opportunistic infection (including tuberculosis), active and latent tuberculosis that occurred in the pooled population from the 7 phase II/III studies are shown in Table 65 (up to Week 12) and Table 66 (overall treatment period).

During the overall treatment period, opportunistic infection (including tuberculosis) occurred in 13 subjects: 4 subjects in the 100 mg-treated subjects (tuberculosis, pulmonary tuberculosis/meningitis tuberculous, oesophageal candidiasis, and lymph node tuberculosis), 5 subjects in the 200 mg-treated subjects (oesophageal candidiasis in 2 subjects, herpes zoster disseminated,[36)] oesophageal candidiasis/pneumonia cryptococcal,[36)] and pneumonia cryptococcal), 2 subjects in the adalimumab-treated subjects (tuberculosis and pneumocystis jirovecii pneumonia[36)]), and 2 subjects in the placebo/MTX-treated subjects (pneumonia cryptococcal and pneumocystis jirovecii pneumonia[36)]). A causal relationship to the study drug could not be ruled out for these events except for 1 subject each in the 100 mg- and 200 mg-treated subjects (both had oesophageal candidiasis).

[36)] This event was reported in a Japanese subject.

In the clinical studies, patients with tuberculosis were allowed to participate only if they met the inclusion criteria for tuberculosis.[37)]

During the overall treatment period, active tuberculosis occurred in 4 subjects: 3 subjects in the 100 mg-treated subjects (tuberculosis, pulmonary tuberculosis/meningitis tuberculous, and lymph node tuberculosis) and 1 subject in the adalimumab-treated subjects (tuberculosis). A causal relationship to the study drug could not be ruled out. All of these subjects were participants from geographical regions where the prevalence of tuberculosis is known to be relatively high (India, Thailand, Poland, and China). No active tuberculosis occurred in the Japanese subpopulation.

Latent tuberculosis tended to occur at a higher incidence in the filgotinib-treated subjects compared with that of the adalimumab- and placebo/MTX-treated subjects. However, the data for filgotinib-treated subjects are based on the results of interferon-gamma (IFN-γ) release assays[38)] which were performed when subjects from one of the parent studies (i.e., the FINCH1, FINCH2, and FINCH3 studies) entered the extension study (the FINCH4 study), indicating that the results for adalimumab-treated subjects and placebo/MTX-treated subjects at the completion of the parent studies are not incorporated into the data. An additional analysis was therefore performed for participants of the FINCH4 study who had tested negative by the IFN-γ release assay, had no results, or whose results were undeterminable at the enrollment of the parent study. Compared with those treated with adalimumab or placebo/MTX, the fraction of filgotinib-treated subjects who tested positive by the IFN-γ release assay at the completion of the parent study did not tend to be higher (5.2% [46 of 877] of subjects in the filgotinib-treated subjects and 8.7% [26 of 299] of subjects in the adalimumab- or placebo/MTX-treated subjects).

On the basis of the above, caution statement will be provided regarding the risk of developing infections associated with filgotinib treatment using the package insert or other materials in a manner equivalent to those implemented for other JAK inhibitors. Post-marketing data on serious infections in clinical use will be collected.

PMDA's view:
In the pooled population from the 7 phase II/III studies, there was no significant increase in the incidence of infections or serious infections in the filgotinib-treated subjects versus placebo/MTX-treated subjects. However, filgotinib inhibits JAK family members involved in immune response. Furthermore, events such as serious infections, opportunistic infections, and active tuberculosis occurred in filgotinib-treated subjects, and the exposure-adjusted number of serious infections for filgotinib was similar to that occurred during the long-term treatment of previously approved JAK inhibitors. Therefore, caution statement regarding the risk for infections associated with filgotinib treatment should be provided in a manner equivalent to those implemented for the previously approved JAK inhibitors. In addition, it is necessary to perform screening for tuberculosis

[37)] Only patients meeting one of the following conditions in (1) through (3) were allowed to enter the study: (1) evidence of active or latent tuberculosis is absent (IFN-γ release assay at screening tested negative, no chest X-ray evidence of active or latent tuberculosis, no medical history of untreated or inadequately treated active or latent tuberculosis); (2) the patient received adequate latent or active tuberculosis treatment in the past; (3) latent tuberculosis was newly identified during screening, appropriate prophylactic therapy for latent tuberculosis was initiated prior to administration of the first dose of the study drug, and is ongoing.
[38)] IFN-γ release assay results became available after the start of filgotinib treatment in the FINCH4 study.

and other evaluations to ascertain the risk for infection before the start of filgotinib administration, and patients should be monitored to ensure suitable management after the start of treatment. In post-marketing investigations, the applicant should gather data on serious infections in clinical use including those that have occurred during long-term treatment and provide the obtained information to healthcare professionals as soon as possible.

2) Herpes zoster and other viral reactivation

The applicant's explanation about the incidence of herpes zoster:

In the clinical studies, patients who had had symptomatic herpes zoster infection within 12 weeks before screening and patients who had a medical history of herpes zoster disseminated or herpes zoster complications (herpes zoster multi-dermatomal, ophthalmic herpes zoster, herpes zoster of the central nervous system, and post herpetic neuralgia) were excluded.

Herpes zoster and reactivation of other viruses that occurred in the pooled population from the 7 phase II/III studies are summarized in Table 65 (up to Week 12) and Table 66 (overall treatment period).

In the entire study population, the exposure-adjusted incidence rate of herpes zoster tended to be slightly higher in the 200 mg group-treated subjects than in the other treated subjects. In the Japanese subpopulation, herpes zoster was reported in filgotinib-treated subjects only. The events, the majority of which were localized and non-serious, resolved by discontinuation of the study drug or medical treatment. Six subjects (1 in the 100 mg-treated subjects and 5 in the 200 mg-treated subjects) who developed serious herpes zoster recovered without sequelae.

Table 68 shows the incidence of herpes zoster by subgroup defined by key patient characteristics. While the exposure-adjusted incidence rate tended to be higher in subjects ≥65 years, there were no consistent trends in any subgroup.

Table 68. Incidence of herpes zoster by subgroup defined by patient characteristics (pooled population from the 7 phase II/III studies, overall treatment period)

		100 mg	200 mg	Adalimumab	Placebo/MTX
N		1,647	2,267	325	1,197
Duration of total exposure (patient-years)		2,032.9	4,047.7	290.1	658.5
Entire study population		1.4 (23/1,647) 1.1	3.3 (74/2,267) 1.8	0.6 (2/325) 0.7	0.6 (7/1,197) 1.1
Age	<65 years	1.1 (14/1,320) 0.9	3.0 (56/1,857) 1.7	0.8 (2/258) 0.9	0.5 (5/952) 1.0
	≥65 years	2.8 (9/327) 2.1	4.4 (18/410) 2.7	0 (0/67) 0	0.8 (2/245) 1.5
Race	White	1.2 (14/1,137) 1.0	3.1 (48/1,568) 1.7	0.9 (2/229) 1.0	0.6 (5/806) 1.1
	Asian	2.8 (8/286) 2.2	4.0 (15/372) 3.0	0 (0/65) 0	1.0 (2/209) 1.7
	Black/ African American	1.9 (1/53) 1.5	3.2 (2/63) 2.3	0 (0/10) 0	0 (0/49) 0
	American Indian or Alaska native	0 (0/87) 0	2.6 (3/117) 1.8	0 (0/20) 0	0 (0/72) 0
	Other	0 (0/82) 0	4.3 (6/140) 1.5	0 (0/1) 0	0 (0/51) 0
Body weight	<60 kg	2.1 (8/389) 1.7	3.6 (20/562) 2.1	0 (0/88) 0	0.3 (1/302) 0.6
	≥60 kg and <100 kg	1.3 (14/1,115) 1.0	3.2 (49/1,509) 1.8	0.9 (2/211) 1.0	0.5 (4/787) 0.9
	≥100 kg	0.7 (1/143) 0.5	2.6 (5/196) 1.5	0 (0/26) 0	1.9 (2/108) 3.2
DMARD	None	0 (0/147) 0	3.8 (16/424) 1.6	0 (0/0) 0	0 (0/69) 0
	MTX alone	1.5 (19/1,302) 1.1	2.9 (46/1,610) 1.7	0.7 (2/285) 0.8	0.4 (4/977) 0.7
	Non-MTX cDMARDs	2.4 (1/42) 2.1	5.0 (3/60) 3.1	0 (0/0) 0	0 (0/34) 0
	MTX + cDMARDs	1.9 (3/156) 1.4	5.2 (9/173) 3.7	0 (0/40) 0	2.6 (3/117) 4.5
Concurrent corticosteroid	No	1.3 (13/1,016) 1.1	3.4 (50/1,486) 1.7	1.1 (2/185) 1.2	0.4 (3/726) 0.8
	Yes	1.6 (10/631) 1.1	3.1 (24/781) 2.2	0 (0/140) 0	0.8 (4/471) 1.5

Upper row, % (n/N of the subgroup); lower row, number of events per 100 person-years (PY) adjusted by duration of total exposure

Although there are limitations in comparing the studies, the exposure-adjusted incidence rate of herpes zoster in filgotinib-treated subjects in the pooled population from the 7 phase II/III studies (overall treatment period) did not tend to be higher than the incidence rates of herpes zoster in the long-term studies of previously approved JAK inhibitors in patients with RA: 3.4 events/100 PY for tofacitinib (*Arthritis Res Ther*. 2019;21:89) and 3.2 events/100 PY for baricitinib (*J Rheumatol*. 2019;46:7-18). An analysis of clinical data in the US indicates that, while no pathological mechanism of action has been identified, the risk for herpes zoster is estimated to be approximately 2-fold higher in tofacitinib-treated patients with RA than that in biologic-treated patients with RA (*Ann Rheum Dis.* 2016;75:1843-7).

The incidence of reactivation of other viruses was similar across all treated subjects, and all the events were herpes simplex virus infection.

On the basis of the above, caution statement will be provided to reduce the risk for herpes zoster and other infections associated with filgotinib treatment using the package insert or other materials in a manner equivalent to those implemented for other JAK inhibitors.

PMDA's view:

There was a trend towards increasing incidence of herpes zoster in the 200 mg-treated subjects in the pooled population from the 7 phase II/III studies. In addition, a similar trend was observed in the Japanese subpopulation, and herpes zoster occurred only in subjects treated with filgotinib. These findings indicate that caution statement should be provided in a manner equivalent to that provided for previously approved JAK inhibitors on the risk for viral reactivation including the reactivation of herpes viruses associated with filgotinib treatment, and on the need for close monitoring for any sign of viral reactivation or development of symptoms after administration of filgotinib so as to allow early detection and to take appropriate measures [see the next section also for reactivation of hepatitis B and C viruses].

It is also known that the risk of herpes zoster in patients treated with JAK inhibitors is higher in Japan and some parts of Asia than in Europe and America (*Arthritis Rheumatol.* 2014;66:2675-84, *Arthritis Rheumatol.* 2017;69:1960-8, and *Rheumatology*. 2019;58:i34-i42). Data from the pooled population from the 7 phase II/III studies show trends of increasing incidence of herpes zoster in the Japanese subpopulation (Table 66) and in other Asian subjects (Table 68) as well. Furthermore, the subgroup analysis of the pooled population shows a trend of increasing incidence of herpes zoster in subjects aged ≥65 years. Given the high proportion of elderly persons treated in clinical practice in Japan, extra caution should be exercised regarding the risk of herpes zoster when treating this population with filgotinib.

3) Hepatitis B- or C-related events

The applicant's explanation about the incidence of hepatitis B- or C-related events:

Of the 7 clinical studies used in the safety analysis in Section 7.R.3, only the 4 phase III studies (the FINCH1, FINCH2, FINCH3, and FINCH4 studies) allowed participation of patients who had been previously infected with hepatitis B virus (HBV)[39] or hepatitis C virus (HCV).[40] Therefore, pooled analyses were performed using data from the 4 studies (pooled population of the 4 phase III studies) to investigate hepatitis B- or C-related events. These subjects were monitored by HBV deoxyribonucleic acid (DNA) or HCV ribonucleic acid (RNA) testing according to the schedule.

Table 69 shows the incidence of hepatitis B-related events[41] and hepatitis C-related events[42] in the pooled population of the 4 phase III studies. While no hepatitis C-related events occurred, hepatitis B-related events occurred only in those subjects who had tested positive for HBc antibodies or HBs antibodies at baseline.

[39] HBc antibody positive or HBs antibody positive, and HBs antigen negative and HBV DNA negative

[40] HCV antibody positive and HCV RNA negative

[41] Events that include the following PTs: acute hepatitis B, hepatitis B, hepatitis B reactivation, HBV-DNA polymerase increased, hepatitis B antibody abnormal, hepatitis B antibody positive, hepatitis B antigen positive, hepatitis B core antigen positive, hepatitis B DNA assay positive, hepatitis B DNA increased, hepatitis B e antigen positive, hepatitis B surface antigen positive, hepatitis B virus test positive, and hepatitis B core antibody positive

[42] Events that include the following PTs: acute hepatitis C, hepatitis C, hepatitis C antibody positive, hepatitis C core antibody positive, hepatitis C RNA fluctuation, hepatitis C RNA increased, hepatitis C RNA positive, and hepatitis C virus test positive

Table 69. Incidence of hepatitis B-related events and hepatitis C-related events (pooled population of the 4 phase III studies, overall treatment period)

	HBc antibody positive or HBs antibody positive				Other than those shown left			
	100 mg	200 mg	Adalimumab	Placebo/ MTX	100 mg	200 mg	Adalimumab	Placebo/ MTX
Hepatitis B-related events	4.0 (6/149)	4.0 (7/174)	2.3 (1/43)	1.6 (2/122)	0 (0/1,221)	0 (0/1,602)	0 (0/282)	0 (0/917)
	HCV antibody positive				Other than those shown left			
	100 mg	200 mg	Adalimumab	Placebo/ MTX	100 mg	200 mg	Adalimumab	Placebo/ MTX
Hepatitis C-related events	0 (0/5)	0 (0/11)	0 (0/0)	0 (0/9)	0 (0/1,365)	0 (0/1,765)	0 (0/325)	0 (0/1,030)

% (n/N of the subgroup)

On the basis of the above, the following caution statement should be provided using the package insert or other materials in a manner equivalent to those implemented for other JAK inhibitors: reactivation of hepatitis B-virus associated with filgotinib treatment has been reported; prior to the start of filgotinib treatment, the patients should be tested for hepatitis B virus infection; and when filgotinib is administered to the carrier of or patient previously infected with hepatitis B virus, the patient should be adequately monitored.

PMDA's view:
Because hepatitis B-related events were reported in the clinical studies in subjects who had been infected with HBV, the patient should be monitored for reactivation of hepatitis B virus during treatment with filgotinib, and relevant caution statement should be adequately provided as explained by the applicant.

(b) Malignancy

The applicant's explanation about the incidence of malignancy:
Malignancy (excluding non-melanoma skin cancer [NMSC]) that occurred in the pooled population from the 7 phase II/III studies is shown in Table 65 (up to Week 12) and Table 66 (overall treatment period). There are no clear differences across treatments either in the entire study population data or in the Japanese subpopulation data.

The standardized incidence ratio (SIR) of malignancy (excluding NMSC) and its 95% CI for the pooled population from the 7 phase II/III studies adjusted by sex, age, and exposure using the general population data from the US National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program were 0.7 [0.3, 1.2] in the 100 mg-treated subjects and 0.8 [0.5, 1.1] in the 200 mg-treated subjects. The SIR of malignancy (excluding NMSC) and the 95% CI for the previously approved JAK inhibitors were 1.17 [0.96, 1.41] for tofacitinib (*Ann Rheum Dis.* 2016;75:831-41) and 1.04 [0.79, 1.36] for baricitinib (*J Rheumatol.* 2019;46:7-18). Although there are limitations in comparing the studies, these values are similar to those of filgotinib-treated subjects in the pooled population from the 7 phase II/III studies.

Patients with RA are reported to have an approximately 2-fold increase in the risk of developing malignant lymphoma compared with a population without RA (*Arthritis Res Ther*. 2015;17:212). The exposure-adjusted incidence rate of malignant lymphoma in the pooled population from the 7 phase II/III studies was 0.1 events/100 PY for the100 mg and 200 mg-treated subjects, which was similar to the incidence rates reported in long-term studies of previously approved JAK inhibitors in patients with RA: 0.1 events/100 PY for

tofacitinib (*Arthritis Res Ther*. 2019;21:89) and 0.09 events/100 PY for baricitinib (*Arthritis Rheumatol*. 2017;69: suppl 10). Malignant lymphoma was not reported in the Japanese subpopulation.

Accordingly, although no firm conclusion can be reached so far with regard to the association between filgotinib treatment and the development of malignancy, caution statement will be provided regarding the occurrence of malignancy using the package insert and other materials in a manner equivalent to those implemented for other JAK inhibitors. Post-marketing data on malignancy in clinical use will be collected.

PMDA's view:
Currently, the available data are limited; in addition, malignancy occurs less frequently and time to onset is relatively long; therefore, it is difficult to come to a firm conclusion regarding the risk of developing malignancy. In view of the various factors including the pharmacological action of filgotinib, the possibility of increased cancer risk due to prolonged immunosuppressive state caused by RA therapies including filgotinib cannot be ruled out. Given that the incidence of malignancy associated with filgotinib treatment is similar to that of previously approved JAK inhibitors, caution regarding the risk of malignancy associated with filgotinib treatment should be provided as a cautionary statement such as "WARNINGS" in the package insert in a manner equivalent to those implemented for the previously approved JAK inhibitors. In addition, information on the incidence of malignancy associated with filgotinib treatment including data on long-term treatment should be continuously collected, and the risk of malignancy should be monitored via post-marketing surveillance.

(c) Dyslipidaemia and major adverse cardiovascular events (MACE)
The applicant's explanation about the incidence of dyslipidaemia and MACE:
Dyslipidaemia and MACE that occurred in the pooled population from the 7 phase II/III studies are summarized in Table 65 (up to Week 12) and Table 66 (overall treatment period).

In the entire study population, the exposure-adjusted incidence rate of dyslipidaemia was higher in the 200 mg-treated subjects than in the MTX/adalimumab-treated subjects. In the Japanese subpopulation, the exposure-adjusted incidence rate tended to be higher in the 100 mg-treated subjects as well as in the 200 mg-treated subjects. Table 70 shows the incidence of abnormal laboratory lipid parameters in the pooled population from the 7 phase II/III studies. Compared with placebo/MTX-treated subjects, an increased number of subjects treated with filgotinib had abnormal laboratory lipid parameters with higher grades of severity; however, these were likely to have been caused by changes in lipid profiles, which were reported in patients with RA who were treated with anti-IL-6 inhibitors or JAK inhibitors that block IL-6 (*Arthritis Care Res.* 2019;71:1004-18).

Table 70. Incidence of abnormal laboratory lipid parameters (pooled population from the 7 phase II/III studies, overall treatment period)

		100 mg	200 mg	Adalimumab	Placebo/MTX
N		1,537	2,127	318	1,090
High cholesterol (in the fasting condition)	Grade 1	103 (6.7)	258 (12.1)	6 (1.9)	38 (3.5)
	Grade 2	55 (3.6)	172 (8.1)	9 (2.8)	19 (1.7)
	Grade 3	1 (<0.1)	11 (0.5)	0	0
	Grade 4	1 (<0.1)	0	0	0
High triglycerides (in the fasting condition)	Grade 1	263 (17.1)	395 (18.6)	43 (13.5)	170 (15.6)
	Grade 2	60 (3.9)	118 (5.5)	11 (3.5)	24 (2.2)
	Grade 3	7 (0.5)	24 (1.1)	0	6 (0.6)
	Grade 4	4 (0.3)	1 (<0.1)	0	0

n (%); see Section 10 for the definition of each Grade

During the overall treatment period, MACE occurred in 38 subjects (13 in the 100 mg-treated subjects, 19 in the 200 mg-treated subjects, 1 in the adalimumab-treated subjects, and 5 in the placebo/MTX-treated subjects). Among these subjects, the outcome was reported as "death" in 10 subjects (4 in the 100 mg-treated subjects and 6 in the 200 mg-treated subjects). All the subjects who developed MACE had at least one of the following cardiovascular risk factors at baseline: hypertension, advanced age, obesity, smoking, dyslipidaemia, diabetes mellitus, and past history of cardiovascular lesions/ischemic central nervous system vascular disorder.

Although there are limitations in comparing the studies, the exposure-adjusted incidence rate of MACE in the long-term studies of previously approved JAK inhibitors in patients with RA was 0.4 events/100 PY for tofacitinib (*Arthritis Res Ther.* 2019;21:89) and 0.5 events/100 PY for baricitinib (*J Rheumatol.* 2019;46:7-18) and was similar to that in filgotinib-treated subjects in the pooled population from the 7 phase II/III studies.

While MACE occurred in filgotinib-treated subjects, all of the subjects had at least 1 cardiovascular risk factors; and patients with RA have an increased cardiovascular risk of approximately 1.7-fold to 2-fold compared with the general population (*Arthritis Rheum.* 2009;61:1571-9 and *Ann Rheum Dis.* 2017;76:1396-404), it is considered that there is no definitive relationship between filgotinib treatment and the occurrence of MACE.

PMDA's view:

In the pooled population from the 7 phase II/III studies, dyslipidaemia tended to increase in the 200 mg-treated subjects compared with the placebo/MTX-treated subjects, the incidence of abnormal laboratory lipid parameters was higher among filgotinib-treated subjects, and Grade ≥3 events occurred primarily in filgotinib-treated subjects. In addition, changes in lipid profiles were reported in patients with RA who were treated with previously approved JAK inhibitors; therefore, caution statement should be provided regarding the risk of developing dyslipidaemia associated with filgotinib treatment as well as guidance including periodical testing and monitoring of lipid parameters during treatment using the package insert or other materials.

Although no clear association of MACE with filgotinib treatment has been identified so far, the possibility that abnormal laboratory lipid parameters after filgotinib treatment mentioned above could increase MACE risk cannot be ruled out. After the market launch, the applicant should continue to collect post-marketing data as well as published literature data on the incidence of MACE associated with filgotinib treatment including data

on long-term treatment. The information obtained should be communicated to healthcare professionals, as necessary.

(d) Venous thromboembolism (VTE)

The applicant's explanation about the incidence of venous thromboembolism (VTE):

Venous thromboembolism that occurred in the pooled population from the 7 phase II/III studies is summarized in Table 65 (up to Week 12) and Table 66 (overall treatment period). There are no clear differences across treatments either in the entire study population data or in the Japanese subpopulation data. The incidence rate of VTE-related events in patients with RA is reported to be 0.61 events/100 PY, an approximately 2.4-fold higher than that of the non-RA population (*Arthritis Care Res.* 2013;65(10):1600-7). The incidence rates in filgotinib-treated subjects in the pooled population from the 7 phase II/III studies did not tend to be higher than the above reported rate.

During the overall treatment period, VTE occurred in 14 subjects (1 in the 100 mg-treated subjects, 8 in the 200 mg-treated subjects, 1 in the adalimumab-treated subjects, and 4 in the placebo/MTX-treated subjects), and the outcome was reported as "death" in 1 of the subjects in the 200 mg-treated subjects. In addition to the 14 subjects, VTE was also reported in 1 subject in the 100 mg BID group in Study GLPG0634-CL-205, and 1 subject in the filgotinib 200 mg single-dose group in Study GS-US-417-3900, a foreign phase I study in healthy subjects. The outcome was reported as "death" in 1 of the subjects in the 100 mg BID group of Study GLPG0634-CL-205. All the subjects who developed VTE during filgotinib treatment had at least one of the following thromboembolism risk factors: obesity, dyslipidaemia, advanced age, current or past nicotine use, inability of body movement, oral contraceptive use, prior history of VTE, and malignancy.

On the basis of the above, although the data so far suggest that there is no increased VTE risk associated with filgotinib treatment, VTE has been reported in filgotinib-treated subjects and VTE is a known safety concern in patients treated with previously approved JAK inhibitors. Therefore, it is considered that there is a potential risk of VTE in patients treated with filgotinib.

PMDA's view:

In the clinical studies, VTE occurred in a limited number of subjects with no increased incidence rate in filgotinib-treated subjects. However, given that deaths were reported in some subjects, caution statement should be provided regarding the risk of VTE in a manner equivalent to those implemented for other JAK inhibitors. After the market launch, the applicant should continue to collect post-marketing data as well as published literature data on the incidence of VTE in clinical use and provide the information obtained to healthcare professionals, as necessary.

(e) Gastrointestinal perforations

The applicant's explanation about the incidence of gastrointestinal perforation-related events:

Gastrointestinal perforation-related events that occurred in the pooled population from the 7 phase II/III studies are summarized in Table 65 (up to Week 12) and Table 66 (overall treatment period). The events were reported

only in 3 subjects in the 200 mg-treated subjects (duodenal ulcer perforation,[36] gastric perforation, and diverticular perforation). All of these were classified as serious events, and a causal relationship to the study drug could not be ruled out for duodenal ulcer perforation and gastric perforation.

Although there are limitations in comparing the studies, the exposure-adjusted incidence rate of gastrointestinal perforation-related events in the 200 mg-treated subjects in the pooled population from the 7 phase II/III studies was similar to the incidence rates reported in long-term studies of previously approved JAK inhibitors in patients with RA: 0.1 events/100 PY for tofacitinib (*Arthritis Res Ther.* 2019;21:89) and 0.05 events/100 PY for baricitinib (*J Rheumatol.* 2019;46:7-18).

The above data indicate that there is no increased risk of gastrointestinal perforation associated with filgotinib treatment at present.

PMDA's view
In the clinical studies, serious gastrointestinal perforation-related events occurred only in subjects treated with filgotinib, and a causal relationship to the study drug could not be ruled out for some events. In addition, given the pharmacological action of filgotinib, an inhibitor of signaling mediated by cytokines such as IL-6, caution statement regarding the risk for gastrointestinal perforation associated with filgotinib treatment should be provided in a manner equivalent to those implemented for the previously approved JAK inhibitors. In addition, the applicant should caution healthcare professionals to carefully consider the benefit-risk balance of filgotinib treatment for patients with diverticulum of the intestine, one of the risk factors for gastrointestinal perforation, before determining the appropriateness of the use of the treatment.

Furthermore, it is expected that treatment of patients with RA involves administration of drugs in combination such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, which have a risk of developing gastrointestinal perforation, and the risk of increasing the incidence of gastrointestinal perforation by coadministration of these drugs should also be investigated. The applicant should continue to collect data on gastrointestinal perforation associated with filgotinib treatment and provide the obtained information to healthcare professionals, as necessary.

(f) Interstitial lung disease

The applicant's explanation about the incidence of interstitial lung disease:
Interstitial lung disease that occurred in the pooled population from the 7 phase II/III studies is summarized in Table 65 (up to Week 12) and Table 66 (overall treatment period). There are no clear differences across treated subjects. Interstitial lung disease did not occur among filgotinib-treated subjects in the Japanese subpopulation.

During the overall treatment period, interstitial lung disease occurred in 21 subjects (6 in the 100 mg-treated subjects, 13 in the 200 mg-treated subjects, and 2 in the placebo/MTX-treated subjects). Over half of the events (11 subjects) were pulmonary fibrosis, and a causal relationship to the study drug was ruled out for the majority of events (10 subjects), which were likely to be the result of medical history or the effect of coadministered

drugs. Serious events occurred in 5 subjects (4 in the 200 mg-treated subjects and 1 in the placebo/MTX-treated subjects), and the outcome was reported as "death" in 2 subjects in the 200 mg-treated subjects. A causal relationship to the study drug was ruled out for one of the events in 1 subject in the 200 mg-treated subjects but could not be ruled out for the events that occurred in 4 subjects.

On the basis of the above, the incidence of interstitial lung disease in the pooled population from the 7 phase II/III studies in filgotinib-treated subjects is similar to that in placebo/MTX-treated subjects. Given that filgotinib-treated subjects who experienced serious or severe interstitial lung disease had known risk factors, it is considered there is no clear association between interstitial lung disease and filgotinib treatment.

PMDA's view:
For some of the serious events of interstitial lung disease reported in the clinical studies, a causal relationship to the study drug could not be ruled out. In addition, the events resulted in death in 2 subjects in the 200 mg-treated subjects. Caution statement regarding the risk for interstitial lung disease associated with filgotinib treatment should be provided in a manner equivalent to those implemented for the previously approved JAK inhibitors. The applicant should also caution healthcare professionals to carefully consider the benefit-risk balance of filgotinib treatment for patients with a prior history of interstitial lung disease before determining the appropriateness of the use of the treatment.

While no interstitial lung disease occurred among filgotinib-treated subjects in the Japanese subpopulation in the pooled population from the 7 phase II/III studies, it has been reported that the incidence of drug-induced lung injury is higher in Japanese than non-Japanese people (*The JRS Guidelines for the Management of Drug-induced Lung Disease.* 2nd edition, Medical Review Co., Ltd. 2018;7-10); therefore, the applicant should continue to collect post-marketing data as well as published literature data on the incidence of interstitial lung disease in clinical use. The information obtained should be communicated to healthcare professionals, as necessary.

(g) Muscle disorder-related events

The applicant's explanation about the incidence of muscle disorder-related events:
Creatine phosphokinase (CPK) increased and muscle disorder that occurred in the pooled population from the 7 phase II/III studies are shown in Table 65 (up to Week 12) and Table 66 (overall treatment period). Rhabdomyolysis occurred in 1 subject in the 200 mg-treated subjects; however, no CPK increased was detected by laboratory tests. A causal relationship to the study drug was denied for this event, and the outcome was reported as "resolved."

Table 71 shows the incidence of CPK increased detected by laboratory tests in the pooled population from the 7 phase II/III studies (overall treatment period). The majority of events were Grade 1 or 2 in severity, asymptomatic, and transient. The incidence of muscle symptom- or muscle disorder-related adverse events in subjects with Grade ≥1 CPK increased was 2.9% (10 of 345) of subjects in the 100 mg-treated subjects, 2.3% (15 of 663) of subjects in the 200 mg-treated subjects, 1.6% (1 of 61) of subjects in the adalimumab-treated

subjects, and 0.9% (1 of 107) of subjects in the placebo/MTX-treated subjects. Only muscle symptom-related events (myalgia or muscle spasms) were observed. All of the events were non-serious and a causal relationship to the study drug was denied except for myalgia in 1 subject in the 200 mg-treated subjects.

Table 71. Incidence of CPK increased detected by laboratory tests (pooled population from the 7 phase II/III studies, overall treatment period)

	Entire study population				Japanese subpopulation			
	100 mg	200 mg	Adalimumab	Placebo/MTX	100 mg	200 mg	Adalimumab	Placebo/MTX
N	1,363	1,769	324	1,031	107	124	28	76
Grade 1	286 (21.0)	569 (32.2)	56 (17.3)	89 (8.6)	21 (19.6)	38 (30.6)	8 (28.6)	6 (7.9)
Grade 2	41 (3.0)	65 (3.7)	4 (1.2)	12 (1.2)	6 (5.6)	4 (3.2)	1 (3.6)	0
Grade 3	11 (0.8)	18 (1.0)	1 (0.3)	6 (0.6)	1 (0.9)	0	0	0
Grade 4	7 (0.5)	11 (0.6)	0	0	1 (0.9)	1 (0.8)	0	0

n (%); see Section 10 for the definition of each Grade

On the basis of the above, the incidence of CPK increased was higher among filgotinib-treated subjects compared with placebo/MTX-treated subjects, the majority of which were asymptomatic despite laboratory tests showing abnormality and obvious muscle symptoms were absent. Therefore, filgotinib treatment is not considered to be clearly associated with the risk of CPK increased that is accompanied by muscle-related events.

PMDA's view:

In the clinical studies, CPK increased occurred in filgotinib-treated subjects in a dose-dependent manner compared with placebo/MTX. Although current data do not necessarily suggest a frequent occurrence of CPK increased accompanied by muscle symptoms or muscle disorder, some cases of CPK increased that occurred in filgotinib-treated subjects were classified as higher grades of severity including Grade 4, and it is not clear how the muscles would be affected if severe CPK increased had persisted in long-term treatment with filgotinib. Therefore, caution statement should be provided regarding the risk of CPK increased in a manner equivalent to those implemented for the previously approved JAK inhibitors. The applicant should also continue to collect post-marketing data as well as published literature data on the incidence of CPK increased and muscle disorders such as rhabdomyolysis and myopathy in clinical use, and provide the obtained information to healthcare professionals, as necessary.

(h) Myelosuppression

The applicant's explanation about the incidence of myelosuppression-related events:

Cytopenia-related events that occurred in the pooled population from the 7 phase II/III studies are shown in Table 65 (up to Week 12) and Table 66 (overall treatment period). Up to Week 12, the incidence and exposure-adjusted incidence rate of neutrophil count decreased-related events in the filgotinib groups tended to be higher than those in the placebo/MTX group; however, other than that, there were no clear differences between respective treated subjects.

Table 72 shows the incidence of abnormal blood cell parameters in the pooled population from the 7 phase II/III studies (overall treatment period). The incidence of Grade ≥1 abnormalities in white blood cell count decreased, neutrophil count decreased, and lymphocyte count decreased was higher in filgotinib-treated subjects than in placebo/MTX-treated subjects, and dose-dependency was also observed.

Table 72. Incidence of abnormal blood cell parameters (pooled population from the 7 phase II/III studies, overall treatment period)

	Entire study population				Japanese subpopulation			
	100 mg	200 mg	Adalimumab	Placebo/MTX	100 mg	200 mg	Adalimumab	Placebo/MTX
N	1,640	2,256	324	1,188	107	124	28	76
White blood cell count decreased								
Grade 1	153 (9.3)	322 (14.3)	34 (10.5)	77 (6.5)	21 (19.6)	37 (29.8)	6 (21.4)	5 (6.6)
Grade 2	50 (3.0)	127 (5.6)	19 (5.9)	28 (2.4)	8 (7.5)	14 (11.3)	5 (17.9)	3 (3.9)
Grade 3	7 (0.4)	8 (0.4)	0	1 (<0.1)	0.	1 (0.8)	0	0
Grade 4	0	1 (<0.1)	0	0	0	1 (0.8)	0	0
Neutrophil count decreased								
Grade 1	125 (7.6)	233 (10.3)	55 (17.0)	55 (4.6)	17 (15.9)	24 (19.4)	8 (28.6)	3 (3.9)
Grade 2	34 (2.1)	132 (5.9)	27 (8.3)	25 (2.1)	5 (4.7)	10 (8.1)	2 (7.1)	3 (3.9)
Grade 3	15 (0.9)	18 (0.8)	1 (0.3)	4 (0.3)	0	2 (1.6)	1 (3.6)	0
Grade 4	3 (0.2)	2 (<0.1)	0	0	0	1 (0.8)	0	0
Lymphocyte count decreased								
Grade 1	39 (2.4)	101 (4.5)	9 (2.8)	49 (4.1)	3 (2.8)	5 (4.0)	0	6 (7.9)
Grade 2	146 (8.9)	334 (14.8)	20 (6.2)	94 (7.9)	14 (13.1)	29 (23.4)	4 (14.3)	7 (9.2)
Grade 3	31 (1.9)	67 (3.0)	3 (0.9)	13 (1.1)	3 (2.8)	10 (8.1)	0	1 (1.3)
Grade 4	2 (0.1)	1 (<0.1)	0	0	0.	0	0	0
Haemoglobin decreased								
Grade 1	236 (14.4)	357 (15.8)	47 (14.5)	233 (19.6)	12 (11.2)	22 (17.7)	5 (17.9)	19 (25.0)
Grade 2	107 (6.5)	106 (4.7)	17 (5.2)	87 (7.3)	6 (5.6)	5 (4.0)	2 (7.1)	4 (5.3)
Grade 3	8 (0.5)	23 (1.0)	3 (0.9)	11 (0.9)	0	1 (0.8)	0	1 (1.3)
Grade 4	0	0	0	0	0	0	0	0
Platelet count decreased[a)]								
Grade 1	57 (3.5)	100 (4.4)	9 (2.8)	32 (2.7)	5 (4.7)	5 (4.0)	0	1 (1.3)
Grade 2	2 (0.1)	2 (<0.1)	1 (0.3)	1 (<0.1)	0	0	0	0
Grade 3	1 (<0.1)	2 (<0.1)	0	0	0	0	0	0
Grade 4	2 (0.1)	1 (<0.1)	0	1 (<0.1)	0	0	0	0

n (%); see Section 10 for the definition of each Grade

a) In the entire study population, the number of subjects evaluated was 1,639 (100 mg-treated subjects) and 1,187 (placebo/MTX-treated subjects)

Table 73 shows the change from baseline in blood cell parameters in the pooled population from the 7 phase II/III studies (overall treatment period). White blood cell count, neutrophil count, and platelet count tended to decrease in filgotinib-treated subjects compared with placebo/MTX-treated subjects, and the trend was consistent throughout the study period. For haemoglobin and lymphocyte count, there were no clear differences between treated subjects.

Table 73. Blood cell parameters over time (pooled population from the 7 phase II/III studies)

	Entire study population				Japanese subpopulation			
	100 mg	200 mg	Adalimumab	Placebo/MTX	100 mg	200 mg	Adalimumab	Placebo/MTX
White blood cell count (× 10^3/μL)								
Week 12	−0.83 ± 2.15 (1,234)	−1.20 ± 2.19 (1,824)	−0.89 ± 2.09 (314)	−0.28 ± 2.01 (1,018)	−0.80 ± 1.47 (77)	−1.32 ± 1.65 (97)	−0.62 ± 1.36 (28)	−0.44 ± 1.53 (72)
Week 52	−1.22 ± 2.19 (583)	−1.56 ± 2.28 (1,308)	−0.95 ± 2.39 (267)	−0.99 ± 2.26 (311)	−1.12 ± 1.70 (46)	−1.76 ± 2.21 (63)	−1.06 ± 1.47 (21)	−2.14 ± 1.87 (19)
Neutrophil count (× 10^3/μL)								
Week 12	−0.75 ± 1.92 (978)	−1.01 ± 1.97 (1,372)	−1.17 ± 2.01 (314)	−0.20 ± 1.82 (960)	−0.77 ± 1.43 (77)	−1.25 ± 1.59 (97)	−0.86 ± 1.23 (28)	−0.39 ± 1.53 (72)
Week 52	−0.97 ± 1.97 (570)	−1.10 ± 2.01 (908)	−1.31 ± 2.25 (267)	−0.76 ± 2.06 (311)	−0.99 ± 1.66 (46)	−1.44 ± 2.16 (63)	−1.34 ± 1.41 (21)	−1.83 ± 1.89 (19)
Lymphocyte count (× 10^3/μL)								
Week 12	−0.01 ± 0.64 (1,233)	0.00 ± 0.64 (1,824)	0.31 ± 0.55 (314)	−0.07 ± 0.55 (1,018)	0.01 ± 0.32 (77)	0.01 ± 0.35 (97)	0.28 ± 0.28 (28)	−0.03 ± 0.31 (72)
Week 52	−0.19 ± 0.58 (583)	−0.19 ± 0.64 (1,308)	0.37 ± 0.61 (267)	−0.18 ± 0.54 (311)	−0.07 ± 0.35 (46)	−0.17 ± 0.35 (63)	0.30 ± 0.32 (21)	−0.19 ± 0.46 (19)
Haemoglobin (g/dL)								
Week 12	0.1 ± 0.90 (1,236)	0.3 ± 1.00 (1,829)	0.2 ± 0.94 (314)	−0.1 ± 0.85 (1,019)	0.3 ± 0.98 (77)	0.2 ± 1.13 (97)	0.2 ± 0.83 (28)	−0.1 ± 0.87 (72)
Week 52	0.3 ± 1.16 (583)	0.5 ± 1.14 (1,311)	0.4 ± 1.02 (267)	0.2 ± 1.14 (311)	0.3 ± 1.15 (46)	0.7 ± 1.37 (63)	0.1 ± 0.50 (21)	0.2 ± 1.18 (19)
Platelet count (× 10^3/μL)								
Week 12	−26 ± 60.3 (1,230)	−31 ± 64.3 (1,815)	−31 ± 61.9 (313)	−4 ± 64.6 (1,009)	−30 ± 61.8 (77)	−41 ± 69.9 (97)	−33 ± 48.0 (28)	−27 ± 62.5 (71)
Week 52	−25 ± 61.9 (582)	−35 ± 72.4 (1,306)	−31 ± 70.5 (265)	−18 ± 88.0 (309)	−37 ± 49.8 (46)	−70 ± 89.6 (63)	−42 ± 50.3 (21)	−68 ± 99.7 (19)

Mean ± standard deviation (N)

Table 74 and Table 75 show the incidence of neutrophil count decreased and lymphocyte count decreased in the pooled population from the 7 phase II/III studies by subgroup of infection/serious infection status. No clear association was observed between the presence/absence of infection and incidence of neutrophil/lymphocyte count decreased.

Table 74. Incidence of neutrophil count decreased and lymphocyte count decreased by infection status (pooled population from the 7 phase II/III studies, entire study population)

Treated Subjects		100 mg		200 mg		Adalimumab		Placebo/MTX	
Infections		No	Yes	No	Yes	No	Yes	No	Yes
N		999	648	1,193	1,074	196	129	873	324
Neutrophil count decreased	Grade 1	71 (7.1)	54 (8.3)	121 (10.1)	112 (10.4)	35 (17.9)	20 (15.5)	39 (4.5)	16 (4.9)
	Grade 2	20 (2.0)	14 (2.2)	61 (5.1)	71 (6.6)	16 (8.2)	11 (8.5)	16 (1.8)	9 (2.8)
	Grade 3	6 (0.6)	9 (1.4)	10 (0.8)	8 (0.7)	0	1 (0.8)	3 (0.3)	1 (0.3)
	Grade 4	2 (0.2)	1 (0.2)	1 (<0.1)	1 (<0.1)	0	0	0	0
Lymphocyte count decreased	Grade 1	18 (1.8)	21 (3.2)	46 (3.9)	55 (5.1)	6 (3.1)	3 (2.3)	36 (4.1)	13 (4.0)
	Grade 2	77 (7.7)	69 (10.6)	145 (12.2)	189 (17.6)	12 (6.1)	8 (6.2)	68 (7.8)	26 (8.0)
	Grade 3	13 (1.3)	18 (2.8)	28 (2.3)	39 (3.6)	0	3 (2.3)	10 (1.1)	3 (0.9)
	Grade 4	2 (0.2)	0	0	1 (<0.1)	0	0	0	0
Serious infections		No	Yes	No	Yes	No	Yes	No	Yes
N		1,596	51	2,200	67	315	10	1,182	15
Neutrophil count decreased	Grade 1	122 (7.6)	3 (5.9)	228 (10.4)	5 (7.5)	54 (17.1)	1 (10.0)	55 (4.7)	0
	Grade 2	33 (2.1)	1 (2.0)	129 (5.9)	3 (4.5)	27 (8.6)	0	25 (2.1)	0
	Grade 3	13 (0.8)	2 (3.9)	18 (0.8)	0	1 (0.3)	0	4 (0.3)	0
	Grade 4	3 (0.2)	0	2 (<0.1)	0	0	0	0	0
Lymphocyte count decreased	Grade 1	37 (2.3)	2 (3.9)	99 (4.5)	2 (3.0)	9 (2.9)	0	49 (4.1)	0
	Grade 2	133 (8.3)	13 (25.5)	326 (14.8)	8 (11.9)	19 (6.0)	1 (10.0)	92 (7.8)	2 (13.3)
	Grade 3	28 (1.8)	3 (5.9)	64 (2.9)	3 (4.5)	3 (1.0)	0	12 (1.0)	1 (6.7)
	Grade 4	2 (0.1)	0	0	1 (1.5)	0	0	0	0

n (%); see Section 10 for the definition of each Grade

Table 75. Incidence of neutrophil count decreased and lymphocyte count decreased by infection status (pooled population from the 7 phase II/III studies, Japanese subpopulation)

Treated Subjects		100 mg		200 mg		Adalimumab		Placebo/MTX	
Infections		No	Yes	No	Yes	No	Yes	No	Yes
N		53	54	43	81	15	13	46	30
Neutrophil count decreased	Grade 1	7 (13.2)	10 (18.5)	9 (20.9)	15 (18.5)	4 (26.7)	4 (30.8)	1 (2.2)	2 (6.7)
	Grade 2	2 (3.8)	3 (5.6)	2 (4.7)	8 (9.9)	0	2 (15.4)	1 (2.2)	2 (6.7)
	Grade 3	0	0	1 (2.3)	1 (1.2)	0	1 (7.7)	0	0
	Grade 4	0	0	0	1 (1.2)	0	0	0	0
Lymphocyte count decreased	Grade 1	1 (1.9)	2 (3.7)	1 (2.3)	4 (4.9)	0	0	4 (8.7)	2 (6.7)
	Grade 2	2 (3.8)	12 (22.2)	8 (18.6)	21 (25.9)	1 (6.7)	3 (23.1)	4 (8.7)	3 (10.0)
	Grade 3	1 (1.9)	2 (3.7)	2 (4.7)	8 (9.9)	0	0	1 (2.2)	0
	Grade 4	0	0	0	0	0	0	0	0
Serious infections		No	Yes	No	Yes	No	Yes	No	Yes
N		104	3	117	7	25	3	73	3
Neutrophil count decreased	Grade 1	17 (16.3)	0	23 (19.7)	1 (14.3)	7 (28.0)	1 (33.3)	3 (4.1)	0
	Grade 2	4 (3.8)	1 (33.3)	10 (8.5)	0	2 (8.0)	0	3 (4.1)	0
	Grade 3	0	0	2 (1.7)	0	1 (4.0)	0	0	0
	Grade 4	0	0	1 (0.9)	0	0	0	0	0
Lymphocyte count decreased	Grade 1	3 (2.9)	0	5 (4.3)	0	0	0	6 (8.2)	0
	Grade 2	13 (12.5)	1 (33.3)	28 (23.9)	1 (14.3)	3 (12.0)	1 (33.3)	7 (9.6)	0
	Grade 3	2 (1.9)	1 (33.3)	10 (8.5)	0	0	0	1 (1.4)	0
	Grade 4	0	0	0	0	0	0	0	0

n (%); see Section 10 for the definition of each Grade

On the basis of the above, the applicant will provide caution statement regarding the risk of neutrophil count decreased associated with filgotinib treatment and guidance on regular monitoring of neutrophil count after the start of treatment using the package insert.

PMDA's view:

In the clinical studies, white blood cell count decreased, neutrophil count decreased, and lymphocyte count decreased occurred in a dose-dependent manner in filgotinib-treated subjects. The incidence of these events tended to be higher in the Japanese subpopulation than in the entire study population. The incidence of haemoglobin decreased was similar among treated subjects; however, in the pooled population from the 7 phase II/III studies, serious anaemia occurred only in filgotinib-treated subjects: 0.2% (4 of 1,647) of subjects in the 100 mg-treated subjects, 0.2% (4 of 2,267) of subjects in the 200 mg-treated subjects, 0% (0 of 325) of subjects in the adalimumab-treated subjects, and 0% (0 of 1,197) of subjects in the placebo/MTX-treated subjects. In addition, there was a risk for myelosuppression expected from the pharmacological action of filgotinib, and therefore patients with blood cell parameters below specified limits were excluded from the clinical studies.

On the basis of the above, caution should be advised in a manner equivalent to that provided for previously approved JAK inhibitors regarding the risk of decrease in blood cell parameters. In addition, guidance on screening prior to filgotinib treatment and periodic monitoring during treatment to minimize the risk of developing adverse events that may be caused by decreased blood cell parameters, and guidance on avoiding filgotinib treatment in patients with low blood cell parameters should be given.

(i) Liver disorder

The applicant's explanation about the incidence of liver disorder:

Liver disorder that occurred in the pooled population from the 7 phase II/III studies is shown in Table 65 (up to Week 12) and Table 66 (overall treatment period). The exposure-adjusted incidence rate did not tend to be higher for filgotinib-treated subjects than for placebo/MTX-treated subjects.

In the overall treatment period, serious liver disorder-related events occurred in 6 subjects (2 subjects in the 100 mg-treated subjects [ascites and hepatotoxicity], 3 subjects in the 200 mg-treated subjects [hepatitis in 2 subjects and ALT increased in 1 subject], and 1 subject in the adalimumab-treated subjects [AST increased/ALT increased]). Among these serious events, a causal relationship to the study drug could not be ruled out for 2 subjects in the 200 mg-treated subjects (ALT increased and hepatitis) and 1 subject in the adalimumab-treated subjects (AST increased/ALT increased). In the Japanese subpopulation, no serious liver disorder-related events occurred.

Table 76 shows the incidence of abnormal liver function parameters in the pooled population from the 7 phase II/III studies (overall treatment period). No subjects met the laboratory test criteria for Hy's Law.

Table 76. Incidence of abnormal liver function parameters (pooled population from the 7 phase II/III studies, overall treatment period)

	Entire study population				Japanese subpopulation			
	100 mg	200 mg	Adalimumab	Placebo/MTX	100 mg	200 mg	Adalimumab	Placebo/MTX
N	1,640	2,256	324	1,189	107	124	28	76
AST								
>3 × ULN	40 (2.4)	84 (3.7)	10 (3.1)	17 (1.4)	4 (3.7)	12 (9.7)	0	0
>5 × ULN	9 (0.5)	20 (0.9)	3 (0.9)	2 (0.2)	0	2 (1.6)	0	0
>10 × ULN	1 (<0.1)	2 (<0.1)	1 (0.3)	1 (<0.1)	0	0	0	0
>20 × ULN	0	1 (<0.1)	0	0	0	0	0	0
ALT								
>3 × ULN	79 (4.8)	123 (5.5)	26 (8.0)	45 (3.8)	6 (5.6)	15 (12.1)	0	5 (6.6)
>5 × ULN	21 (1.3)	41 (1.8)	8 (2.5)	9 (0.8)	2 (1.9)	5 (4.0)	0	0
>10 × ULN	3 (0.2)	8 (0.4)	2 (0.6)	2 (0.2)	0	0	0	0
>20 × ULN	0	1 (<0.1)	0	0	0	0	0	0
Total bilirubin								
>1 × ULN	76 (4.6)	128 (5.7)	22 (6.8)	29 (2.4)	5 (4.7)	6 (4.8)	0	2 (2.6)
>2 × ULN	2 (0.1)	5 (0.2)	1 (0.3)	4 (0.3)	0	1 (0.8)	0	0
ALP								
>1.5 × ULN	40 (2.4)	58 (2.6)	5 (1.5)	29 (2.4)	3 (2.8)	5 (4.0)	0	1 (1.3)

n (%)

On the basis of the above, the incidence of serious liver disorder-related events and abnormal liver function parameters was low in filgotinib-treated subjects. Filgotinib treatment is not considered to be associated with the risk of hepatotoxicity or drug-induced liver injury.

PMDA's view:

Although the incidence rate of liver disorder-related events in the pooled population from the 7 phase II/III studies did not tend to be higher for filgotinib-treated subjects than for placebo/MTX-treated subjects, serious liver disorder-related events occurred only in filgotinib-treated subjects and adalimumab-treated subjects. In addition, events for which a causal relationship to the study drug could not be ruled out also occurred. While liver function laboratory test parameters such as AST and ALT were within the normal range in the majority of subjects, subjects whose laboratory values fell outside the normal range were more likely to be in the filgotinib group rather than the placebo/MTX; in addition, dose-dependency was also observed. Given that

various drugs coadministered in RA therapy may cause liver disorder, caution should be advised regarding the risk of developing liver disorders, and guidance on monitoring of liver function laboratory test parameters during filgotinib treatment should be given. The applicant should also make sure to collect post-marketing data regarding the effect of filgotinib treatment on liver function in clinical use.

(j) Hypophosphataemia

The applicant's explanation about hypophosphataemia:

Hypophosphataemia that occurred in the pooled population from the 7 phase II/III studies is shown in Table 65 (up to Week 12) and Table 66 (overall treatment period). In the overall treatment period, Grade 3 hypophosphataemia occurred in 3 subjects (1 in the 100 mg-treated subjects and 2 in the 200 mg-treated subjects), and Grade 3 blood phosphorus decreased occurred in 1 subject in the 100 mg-treated subjects. All of these events were classified as non-serious and returned to the normal range spontaneously without intervention. Because these subjects had normal serum phosphate levels at baseline, they were diagnosed as having acute hypophosphataemia. It has been suggested that acute hypophosphataemia is associated with underlying factors including hospitalization, chronic alcohol dependence, and chronic obstructive pulmonary disease as well as use of phosphate-binding antacids (*Lancet Diabetes Endocrinol.* 2020;8:163-74). While mild and moderate hypophosphataemia rarely cause major adverse effects, severe acute hypophosphataemia may cause rhabdomyolysis, hematologic complications, and decreased myocardial contraction, and may lead to respiratory failure in the acute phase. None of the filgotinib-treated subjects who developed hypophosphataemia presented with the symptoms shown above.

Table 77 shows the incidence of decreased serum phosphorus levels detected by laboratory tests in the pooled population from the 7 phase II/III studies (overall treatment period). The incidence of decreased serum phosphorus levels was higher in filgotinib-treated subjects than in placebo/MTX-treated subjects, and similar result was obtained also in the Japanese subpopulation.

Table 77. Incidence of decreased serum phosphorus levels detected by laboratory tests (pooled population from the 7 phase II/III studies, overall treatment period)

	Entire study population				Japanese subpopulation			
	100 mg	200 mg	Adalimumab	Placebo/MTX	100 mg	200 mg	Adalimumab	Placebo/MTX
N	1,640	2,256	324	1,189	107	124	28	76
Grade 1	0	0	0	0	0	0	0	0
Grade 2	69 (4.2)	172 (7.6)	9 (2.8)	36 (3.0)	3 (2.8)	11 (8.9)	0	2 (2.6)
Grade 3	26 (1.6)	48 (2.1)	3 (0.9)	6 (0.5)	2 (1.9)	3 (2.4)	0	0
Grade 4	0	1 (<0.1)	0	0	0	0	0	0

n (%); see Section 10 for the definition of each Grade

Decreased serum phosphorus levels detected by laboratory tests was not consistently associated with the occurrence of adverse events that may be related to hypophosphataemia (fracture, muscle disorder, renal disorder, gastrointestinal disorder, respiratory disorder-related events [including chronic obstructive pulmonary disease and respiratory failure], abnormal electrolyte levels including hypercalcaemia).

On the basis of the above findings, hypophosphataemia associated with filgotinib treatment is manageable through routine clinical intervention, and therefore caution statement on hypophosphataemia will not be necessary.

PMDA's view:

While the incidence of hypophosphataemia-related adverse events was low in the clinical studies (Table 66), the incidence of decreased serum phosphorus levels detected by laboratory tests was higher in filgotinib-treated subjects than in placebo/MTX-treated subjects, and dose dependency was also indicated. In addition, decreased serum phosphorus levels lasted for ≥5 months in 2 subjects. The applicant should specify decreased serum phosphorus levels as an "important potential risk" and continue to collect post-marketing data as well as published literature data to investigate the risk for the following reasons: the mechanism of decrease in serum phosphorus levels has not been clarified; clinical symptoms and physical findings caused by hypophosphataemia are nonspecific, thus making it difficult for a patient with hypophosphataemia to be diagnosed unless strongly suspected by the physician; and the serum phosphorus level is a parameter that is not likely to be tested in routine clinical practice for RA. The package insert should include information on the incidence of decreased serum phosphorus levels in clinical studies.

(k) Effects on male fertility

The applicant's explanation about the effects on male fertility:

Data for filgotinib-treated male subjects (N = 725) in the pooled population from the 7 phase II/III studies were analyzed, and adverse events related to or suggestive of male infertility occurred in 13 subjects.[43)] All events were non-serious and classified as follows: adverse events related to change in reproductive hormonal levels in 11 subjects (blood testosterone decreased [7 subjects], blood testosterone free decreased [5 subjects], blood FSH increased [3 subjects], blood LH increased [1 subject], and blood LH decreased [1 subject]) and adverse events related to change in hormonal levels in 2 subjects (hypogonadism and testicular disorder[44)]). In the phase II studies, 26 adverse events related to change in reproductive hormonal levels occurred, and as of the data cut-off date, the events were reported as "resolved" (7 events), "resolved after dose reduction of filgotinib" (8 events), "resolved after interruption/discontinuation of the study drug" (4 events), and "ongoing" (7 events). A causal relationship to the study drug was denied for testicular disorder. Ciprofloxacin was administered to the subject who developed a complication of urinary tract infection, and 4 days later, testicular disorder resolved.

The effects on reproductive hormones were investigated in the phase II studies, which showed no clinically relevant change in reproductive hormone levels over time associated with filgotinib. Anomalies in reproductive hormone levels in each subject were evaluated by the endocrinologist in the data monitoring committee, and the evaluation did not identify any safety signals.

[43)] In the phase II studies (Studies GLPG0634-CL-203, -204, and -205), testosterone, FSH, LH, prolactin, and inhibin B were periodically measured to investigate the effects on reproductive hormones. Of the 13 subjects who had adverse events, 11 subjects were from the phase II studies.

[44)] The reported event was swelling of the right testis.

Clinical studies are currently underway in patients with RA, inflammatory bowel disease, and other conditions to evaluate the potential effect of filgotinib on human semen parameters. The studies are expected to provide us with more detailed information on the effect on male fertility. Currently the risk for human male fertility is not clear.

A statement to the effect that the potential of filgotinib to affect human spermatogenesis and fertility has not been clarified will be included in the "OTHER PRECAUTIONS" section of the package insert together with the findings observed in the non-clinical studies.

PMDA's view:
Although currently available data from clinical studies have not shown symptomatic findings related to human testis and male fertility associated with filgotinib treatment, given the results of non-clinical studies [see Section 5.R.3.1], possible impacts on the testis cannot be ruled out, raising concerns about the risk of a reduction in male fertility. Therefore, when giving filgotinib to male patients, healthcare professionals need to thoroughly inform patients of the risk of impaired spermatogenesis and associated reduction in fertility. When treating male patients who wish their partners to become pregnant, the appropriateness of the use of filgotinib should be carefully determined. Caution should be adequately provided regarding the risk of reduced male fertility accompanied by impaired spermatogenesis associated with filgotinib treatment using the package insert or other materials. The applicant should continue to collect information including data from ongoing clinical studies and provide the obtained information to healthcare professionals as soon as possible.

The above conclusion by PMDA in Section 7.R.3 will be further discussed at the Expert Discussion.

7.R.4 Indication and clinical positioning

7.R.4.1 Indication

The applicant's explanation:
When the application was filed, filgotinib was thought to demonstrate efficacy regardless of prior treatment of RA based on the results of the FINCH1, FINCH2, and FINCH3 studies, and therefore the indication of filgotinib was proposed as "rheumatoid arthritis (including the prevention of structural joint damage)." However, in the FINCH3 study, which was conducted in MTX-naïve patients with RA, a certain level of efficacy was demonstrated with MTX alone. Taking into consideration various factors including the clinical positioning of JAK inhibitors in current RA treatment, which will be discussed later, the indication in the present application was reconsidered and modified to "rheumatoid arthritis in patients who have had an inadequate response to conventional therapies (including the prevention of structural joint damage)." It was also decided to add a cautionary statement in the "PRECAUTIONS CONCERNING INDICATION" section of the package insert to the effect that filgotinib should be used if clear RA-induced symptoms remained unresolved in patients who had received appropriate prior treatment with at least 1 anti-rheumatic drug such as methotrexate.

On the basis of the submitted data, discussions in Sections 7.R.2 and 7.R.3, and the applicant's explanation, PMDA concluded that the indication of filgotinib should be specified as "rheumatoid arthritis in patients who have had an inadequate response to conventional therapies (including the prevention of structural joint damage)" and it is appropriate to caution with a statement to the effect that filgotinib should be used if clear RA-induced symptoms remained unresolved in patients who had received appropriate prior treatment with at least 1 anti-rheumatic drug.

The above conclusion by PMDA will be further discussed at the Expert Discussion.

7.R.4.2 Clinical positioning

The applicant's explanation about the expected clinical positioning of filgotinib:

The RA treatment guidelines issued in Japan, the US, and Europe highly recommended on using treat-to-target (T2T) strategies, which aim at achieving clinical remission or low disease activity depending on the disease duration of each patient (*JCR RA Treatment Guidelines* 2014, *Arthritis Care Res.* 2016;68:1-25, and *Ann Rheum Dis.* 2020;0:1-15). In the EULAR Recommendations for the Management of Rheumatoid Arthritis (*Ann Rheum Dis.* 2020;0:1-15), MTX and other cDMARDs are recommended as first-line treatment options for initial treatment. If appropriate control has not been achieved within 3 to 6 months after the initial therapy with cDMARDs, the patient should be tested using the available prognostic markers. If unfavorable prognostic factors are absent, the patient should switch to a second cDMARD or cDMARDs should be used in combination. If unfavorable prognostic factors are present, use of biologics or addition of JAK inhibitors is recommended. In Japan, treatment has been performed according to the prescribed treatment strategies. Currently, JAK inhibitors, namely, tofacitinib, baricitinib, peficitinib, and upadacitinib have been approved for the indication of RA with inadequate response to conventional therapies.

The clinical studies, which were conducted in patients with RA who had an inadequate response to MTX (the FINCH1 study) or to biologics (the FINCH2 study), demonstrated the efficacy and safety of filgotinib on RA with inadequate response to conventional therapies; therefore, filgotinib can be positioned as a treatment option for patients who had an inadequate response to MTX or other conventional therapies, similarly to previously approved JAK inhibitors. Since combined use of filgotinib with biologics or with other JAK inhibitors was prohibited in the clinical studies of filgotinib, data on filgotinib in combination with such drugs are not available. Therefore, a cautionary statement to the effect that filgotinib should not be used in combination with biologics or other JAK inhibitors will be included in the package insert or other materials.

PMDA's view:

On the basis of the submitted clinical study data and the latest treatment system for RA, filgotinib can be regarded as a treatment option for patients who had an inadequate response to conventional therapies similarly to previously approved JAK inhibitors as explained by the applicant. It is also appropriate to prohibit the use of filgotinib in combination with biologics or other JAK inhibitors. In addition, because filgotinib can be easily administered orally, healthcare professionals should be fully informed of the following requirements: the appropriateness of the use of filgotinib should be determined by a physician with sufficient knowledge and

experience in pharmacotherapy for RA after considering the benefit-risk balance of filgotinib treatment and conventional therapies at a medical institution with adequate facilities to respond to serious infections or other emergencies.

The above conclusion by PMDA will be further discussed at the Expert Discussion.

7.R.5. Dosage and administration

7.R.5.1 Dosage regimen

The applicant's explanation about the proposed dosage regimen of filgotinib:

It was concluded that the dosage regimen of filgotinib should be specified as "the usual adult dosage is 200 mg of filgotinib orally once daily. The dose may be adjusted to 100 mg once daily according to the patient's condition" based on the findings shown below:

- In the FINCH1 and FINCH2 studies, the primary efficacy endpoints, ACR20 at Week 12 (the FINCH1 and FINCH2 studies) and the change from baseline in mTSS at Week 24 (the FINCH1 study) were evaluated. The difference for each of the filgotinib 100 mg and 200 mg groups versus placebo for the endpoints was statistically significant in both studies [see Sections 7.1.1 and 7.1.2].
- The results of clinical studies conducted in Japan and other countries did not reveal any particular safety concerns, with the filgotinib 100 mg and 200 mg groups having similar safety profiles [see Section 7.R.3].
- In the FINCH1 and FINCH2 studies, the proportion of subjects who achieved low disease activity (DAS28-CRP ≤3.2) or remission (DAS28-CRP <2.6, CDAI ≤2.8, ACR/EULAR Boolean Remission), recognized by the international guidelines as important target measures, was higher in the 100 mg group than in the 200 mg group [see Section 7.R.2].
- In the FINCH1 and FINCH2 studies, the efficacy of filgotinib was also higher in the 100 mg group than the placebo group. It is expected that a certain number of patients such as those with severe renal impairment will need low doses [see Section 6.R.2]; therefore, the 100 mg dose needs to be made available depending on the patient's condition.

PMDA's view:

The submitted data, the applicant's explanation, and discussions in Sections 7.R.2 and 7.R.3 have indicated that it is appropriate to specify the usual dosage regimen of filgotinib as 200 mg once daily.

In addition, the efficacy was also higher at filgotinib 100 mg than the placebo. Given that there is concern regarding an increased risk of occurrence of dose-dependent adverse events or fluctuation in laboratory values, and the fact that there are many elderly people and underweight patients in clinical practice in Japan, it is expected that there will be cases where dose adjustment is needed after disease activity and other aspects taken into account. According to the RA guidelines issued in Japan, the US, and Europe, dose reduction of biologics and JAK inhibitors should be considered for patients who maintained remission for a long time while on treatment. It has been reported that dose reduction after maintaining low disease activity or achieving remission status did not impact disease activity control in patients treated with baricitinib, a JAK inhibitor (*Ann Rheum Dis.* 2019;78:171-178).

On the basis of the above, while dose reduction of filgotinib was not investigated during the study period of the clinical studies, it is clinically meaningful to add 100 mg as a treatment option so as to facilitate dose adjustment taking into account the risk of developing adverse reactions and the status of disease activity in individual patient. Therefore, it was concluded that the dosage can be specified.

The above conclusion by PMDA will be further discussed at the Expert Discussion.

7.R.5.2 Dosage regimen of filgotinib in patients with renal impairment

The applicant's explanation about the dosage regimen of filgotinib in patients with renal impairment based on the efficacy and safety data from a clinical pharmacology study in patients with renal impairment [see Section 6.2.2.2] and phase III studies:

Data including the results from the clinical pharmacology study in patients with renal impairment [see Section 6.2.2.2] indicate that it is appropriate to reduce the dose of filgotinib to 100 mg in patients with severe renal impairment [see Section 6.R.2]. In the phase III studies (the FINCH1, FINCH2, and FINCH3 studies), a certain number of patients with mild or moderate renal impairment (CL_{cr} ≥40 mL/min) were also enrolled. The dosage regimen for patients with mild or moderate renal impairment was investigated based on the efficacy and safety results from the phase III studies.

Table 78 shows ACR20 and the proportion of subjects who achieved DAS28-CRP <2.6 by severity of renal impairment at the evaluation timepoint for the primary endpoints in the FINCH1, FINCH2, and FINCH3 studies. In the FINCH1 and FINCH2 studies, the efficacy in patients with moderate renal impairment in each treatment group was similar to that in patients with normal renal function or mild renal impairment.

Table 78. The efficacy results for clinical manifestations of RA by severity of renal impairment (FAS, NRI)

Study	FINCH1			FINCH2			FINCH3		
Patient population	MTX-IR			Biologic-IR			MTX-naïve		
Coadministered drug	MTX			cDMARDs			MTX		
Primary evaluation timepoint	Week 12			Week 12			Week 24		
Renal impairment	Normal	Mild	Moderate	Normal	Mild	Moderate	Normal	Mild	Moderate
ACR20 (primary endpoint)									
100 mg	68.8 (209/304)	71.9 (115/160)	68.8 (11/16)	53.4 (47/88)	63.8 (37/58)	57.1 (4/7)	80.9 (93/115)	81.2 (69/85)	57.1 (4/7)
200 mg	81.3 (239/294)	72.2 (117/162)	44.4 (8/18)	68.8 (55/80)	63.0 (34/54)	61.5 (8/13)	83.3 (205/246)	81.0 (124/153)	47.1 (8/17)
Placebo	49.1 (137/279)	51.9 (95/183)	38.5 (5/13)	35.0 (28/80)	25.9 (15/58)	30.0 (3/10)	71.1 (175/246)	70.9 (107/151)	78.9 (15/19)
200 mg alone[a)]							83.3 (120/144)	70.4 (38/54)	50.0 (6/12)
Proportion of subjects achieving DAS28-CRP <2.6									
100 mg	23.4 (71/304)	25.0 (40/160)	18.8 (3/16)	25.0 (22/88)	25.9 (15/58)	28.6 (2/7)	40.9 (47/115)	48.2 (41/85)	0 (0/7)
200 mg	33.3 (98/294)	35.8 (58/162)	33.3 (6/18)	27.5 (22/80)	16.7 (9/54)	15.4 (2/13)	58.1 (143/246)	52.3 (80/153)	11.8 (2/17)
Placebo	9.3 (26/279)	9.8 (18/183)	0 (0/13)	10.0 (8/80)	6.9 (4/58)	0 (0/10)	30.9 (76/246)	25.2 (38/151)	36.8 (7/19)
200 mg alone[a)]							45.1 (65/144)	40.7 (22/54)	16.7 (2/12)

% (n/N); a) MTX was not coadministered.
See Table 79 for the severity of renal impairment

Table 79 and Table 80 show the summary of safety data by severity of renal impairment in the pooled population from the 7 phase II/III studies (overall treatment period). While the subgroup of patients with moderate renal impairment had a higher incidence of serious adverse events for which a causal relationship to the study drug could not be ruled out, Grade ≥3 adverse events, adverse events leading to study drug discontinuation, adverse reactions, and deaths in the 200 mg group compared with other treatment groups, no statistically significant difference was observed.

The above and the discussion in Section 6.R.2 indicated that, although dose adjustment of filgotinib for patients with mild or moderate renal impairment is not necessary, a dosage regimen of 100 mg once daily would be appropriate for patients with severe renal impairment.

Table 79. Summary of safety data by severity of renal impairment (pooled population from the 7 phase II/III studies, overall treatment period)

	Normal renal function (eGFR ≥90 mL/min/1.73 m^2)			Mild renal impairment (eGFR ≥60 and <90 mL/min/1.73 m^2)			Moderate renal impairment (eGFR ≥30 and <60 mL/min/1.73 m^2)		
	100 mg	200 mg	Placebo/ MTX	100 mg	200 mg	Placebo/ MTX	100 mg	200 mg	Placebo/ MTX-
N	980	1,377	714	609	792	436	58	97	47
Duration of total exposure (patient-years)	1,190.5	2,497.6	386.1	770.9	1,409.2	243.8	71.6	140.9	28.7
All adverse events	672 (68.6) 56.4	1,054 (76.5) 42.2	423 (59.2) 109.6	431 (70.8) 55.9	637 (80.4) 45.2	273 (62.6) 112.0	37 (63.8) 51.7	79 (81.4) 56.1	35 (74.5) 122.2
Serious adverse events	87 (8.9) 7.3	123 (8.9) 4.9	28 (3.9) 7.3	73 (12.0) 9.5	110 (13.9) 7.8	24 (5.5) 9.8	6 (10.3) 8.4	20 (20.6) 14.2	7 (14.9) 24.4
Serious adverse events for which a causal relationship to the study drug could not be ruled out	25 (2.6) 2.1	43 (3.1) 1.7	10 (1.4) 2.6	18 (3.0) 2.3	32 (4.0) 2.3	3 (0.7) 1.2	0 0	9 (9.3) 6.4	0 0
Grade ≥3 adverse events	106 (10.8) 8.9	153 (11.1) 6.1	42 (5.9) 10.9	92 (15.1) 11.9	133 (16.8) 9.4	39 (8.9) 16.0	8 (13.8) 11.2	22 (22.7) 15.6	3 (6.4) 10.5
Adverse events leading to study drug discontinuation	54 (5.5) 4.5	124 (9.0) 5.0	27 (3.8) 7.0	37 (6.1) 4.8	97 (12.2) 6.9	17 (3.9) 7.0	2 (3.4) 2.8	17 (17.5) 12.1	3 (6.4) 10.5
Adverse reactions	283 (28.9) 23.8	496 (36.0) 19.9	171 (23.9) 44.3	186 (30.5) 24.1	293 (37.0) 20.8	120 (27.5) 49.2	9 (15.5) 12.6	36 (37.1) 25.6	10 (21.3) 34.9
Death	2 (0.2) 0.2	8 (0.6) 0.3	0 0	4 (0.7) 0.5	7 (0.9) 0.5	2 (0.5) 0.8	0 0	3 (3.1) 2.1	0 0

Upper row, n (%); lower row, number of events per 100 person-years (PY) adjusted by duration of total exposure

Table 80. Summary of safety data by severity of renal impairment (by SOC)

	Normal renal function (eGFR ≥90 mL/min/1.73 m^2)			Mild renal impairment (eGFR ≥60 and <90 mL/min/1.73 m^2)			Moderate renal impairment (eGFR ≥30 and <60 mL/min/1.73 m^2)		
	100 mg	200 mg	Placebo/ MTX	100 mg	200 mg	Placebo/ MTX	100 mg	200 mg	Placebo/ MTX
N	980	1,377	714	609	792	436	58	97	47
Duration of total exposure (patient-years)	1,190.5	2,497.6	386.1	770.9	1,409.2	243.8	71.6	140.9	28.7
Blood and lymphatic system disorders	76 (7.8) 6.4	125 (9.1) 5.0	39 (5.5) 10.1	45 (7.4) 5.8	76 (9.6) 5.4	20 (4.6) 8.2	4 (6.9) 5.6	15 (15.5) 10.6	1 (2.1) 3.5
Cardiac disorders	31 (3.2) 2.6	52 (3.8) 2.1	8 (1.1) 2.1	21 (3.4) 2.7	42 (5.3) 3.0	9 (2.1) 3.7	3 (5.2) 4.2	8 (8.2) 5.7	3 (6.4) 10.5
Gastrointestinal disorders	198 (20.2) 16.6	321 (23.3) 12.9	116 (16.2) 30.0	140 (23.0) 18.2	198 (25.0) 14.1	83 (19.0) 34.0	11 (19.0) 15.4	23 (23.7) 16.3	10 (21.3) 34.9
Hepatobiliary disorders	24 (2.4) 2.0	52 (3.8) 2.1	11 (1.5) 2.8	19 (3.1) 2.5	26 (3.3) 1.8	9 (2.1) 3.7	1 (1.7) 1.4	3 (3.1) 2.1	0 0
Infections and infestations	381 (38.9) 32.0	636 (46.2) 25.5	188 (26.3) 48.7	248 (40.7) 32.2	385 (48.6) 27.3	116 (26.6) 47.6	19 (32.8) 26.5	52 (53.6) 36.9	20 (42.6) 69.8
Investigations	113 (11.5) 9.5	268 (19.5) 10.7	53 (7.4) 13.7	79 (13.0) 10.2	178 (22.5) 12.6	33 (7.6) 13.5	6 (10.3) 8.4	23 (23.7) 16.3	7 (14.9) 24.4
Renal and urinary disorders	31 (3.2) 2.6	51 (3.7) 2.0	6 (0.8) 1.6	28 (4.6) 3.6	48 (6.1) 3.4	12 (2.8) 4.9	5 (8.6) 7.0	10 (10.3) 7.1	2 (4.3) 7.0
Vascular disorders	54 (5.5) 4.5	98 (7.1) 3.9	24 (3.4) 6.2	45 (7.4) 5.8	84 (10.6) 6.0	19 (4.4) 7.8	2 (3.4) 2.8	11 (11.3) 7.8	2 (4.3) 7.0

Upper row, n (%); lower row, number of events per 100 person-years (PY) adjusted by duration of total exposure

On the basis of the explanation above and discussions in Section 6.R.2, the dosage regimen for patients with severe renal impairment can be specified as 100 mg once daily. However, the dosage regimen for patients with moderate renal impairment should be 100 mg once daily, the same as those with severe renal impairment for the following reasons.

- The results of the clinical pharmacology study in patients with renal impairment [see Section 6.2.2.2] suggested that exposure ($AUC_{0\text{-}24h}$) to GS-829845, an active metabolite, in patients with moderate renal impairment can increase >2-fold compared with patients with normal renal function.

- The efficacy was also higher at filgotinib 100 mg than the placebo. Taking into account the patient's risk of developing adverse reactions and the status of disease activity, the dose level of 100 mg can be a treatment option regardless of renal impairment status [see Section 7.R.5.1].
- In the pooled population from the 7 phase II/III studies (overall treatment period), although safety by severity of renal impairment did not differ significantly between treated subjects, events including serious adverse events for which a causal relationship to the study drug could not be ruled out and Grade ≥3 adverse events occurred frequently in 200 mg-treated subjects with moderate renal impairment. A similar trend was observed for some events in the analysis of adverse events by SOC.

Given that patients with CL_{cr} of <40 mL/min were excluded from the clinical studies, and experience in patients with moderate or severe renal impairment is limited, the applicant should continue to collect safety and efficacy data on patients with renal impairment in the specified use-results survey after the market launch, covering all patients who will be receiving filgotinib and provide the obtained information to healthcare professionals as soon as possible.

The above conclusion by PMDA will be further discussed at the Expert Discussion.

7.R.6 Post-marketing safety measures

The applicant plans to conduct a specified use-results survey covering all patients with RA who will be receiving filgotinib to evaluate the safety and other data including long-term treatment in clinical use after the market launch and gather information on the incidence of events including malignancy and serious infections.

In the package insert, as with the previously approved JAK inhibitors, caution will be provided for the following issues: filgotinib should be used by physicians with sufficient knowledge of filgotinib and experience in RA therapies; risks associated with filgotinib treatment, namely, serious infections (including tuberculosis), malignancy, viral reactivation including reactivation of hepatitis B and herpes viruses, decreases in blood cells, abnormal laboratory values for liver function and lipid parameters, deep vein thrombosis/pulmonary embolism; implementation of appropriate screening before the start of filgotinib treatment, namely, tuberculosis and hepatitis B virus infection. Furthermore, because risk of teratogenicity cannot be ruled out, filgotinib should be contraindicated in women who are or may be pregnant, and caution will be provided regarding the use of effective contraception by women of childbearing potential.

In addition, there is concern regarding the risk of reduced male fertility accompanied by impaired spermatogenesis based on data from the non-clinical studies of filgotinib. The package insert will also include a statement to the effect that it is not known whether filgotinib has the potential to affect spermatogenesis and fertility in humans.

PMDA's view:

As discussed in Section 7.R.3, the safety profiles of filgotinib do not differ significantly from those of the previously approved JAK inhibitors with the exception of the risk of hypophosphataemia and reduction in male

fertility accompanied by impaired spermatogenesis based on currently available clinical study results. Therefore, the risk of filgotinib can be managed by implementing safety measures in a manner equivalent to those implemented for other JAK inhibitors. As for the risk of hypophosphataemia and reduction in male fertility accompanied by impaired spermatogenesis, which are considered to be unique to filgotinib, in addition to providing caution statement in the package insert or other materials, the applicant should continue to collect data after the market launch, provide the obtained information to healthcare professionals as soon as possible, and if necessary, discuss whether further safety measures should be implemented.

It is appropriate to cover all patients with RA who will be receiving filgotinib in the specified use-results survey planned by the applicant in order to update safety profiles during long-term treatment with filgotinib in clinical use accurately and quickly. The safety specifications for the planned specified use-results survey included important identified risks (serious infections, herpes zoster, VTE, gastrointestinal perforations, liver disorder, interstitial lung disease, neutrophil count decreased, lymphocyte count decreased, haemoglobin decreased, and reactivation of hepatitis B virus) and important potential risks (malignancy, cardiovascular events, rhabdomyolysis/myopathy, and hypophosphataemia). However, the incidence of these events is generally low, and therefore it is difficult to investigate their incidence during a limited study period. Accordingly, it is important to assess their incidences over a long period of time wherever possible.

The above conclusion by PMDA and the necessity of further safety measure will be further discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.7, CTD 5.3.5.1.10, CTD 5.3.5.1.11, and CTD 5.3.5.1.12) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that filgotinib has efficacy in the treatment of rheumatoid arthritis in patients who have had an inadequate response to conventional therapies, and that

filgotinib has acceptable safety in view of its benefits. Filgotinib is clinically meaningful because it offers a new treatment option for patients with RA who had an inadequate response to conventional therapies.

Adequate safety measures should be taken, equivalent to those implemented for biologics and JAK inhibitors used in patients with RA, namely, tofacitinib, baricitinib, peficitinib, and upadacitinib because serious adverse reactions such as infections and malignancies may occur. Caution should be provided regarding the risks unique to filgotinib, i.e., hypophosphataemia and reduction in male fertility accompanied by impaired spermatogenesis. In post-marketing surveillance, the safety of filgotinib in clinical use, including data on long-term treatment should be further evaluated.

PMDA has concluded that filgotinib may be approved if it is not considered to have any particular problems based on comments from the Expert Discussion provided that the safety measures above are implemented.

10. Others

The method of efficacy evaluation and definition of endpoints used in the clinical studies of Jyseleca are summarized.

Description	Definition
ACR20, ACR50, or ACR70	**ACR core set measures** (1) Tender joint count in 68 joints (TJC) (2) Swollen joint count in 66 joints (SJC) (3) Patient's pain assessment on a 0-100 mmVAS (4) Patient's global assessment on a 0-100 mmVAS (PtGA) (5) Physician's global assessment on a 0-100 mmVAS (PhGA) (6) Functional status evaluation (Health Assessment Questionnaire-Disability Index, HAQ-DI, questionnaires on functional status specific for RA) (7) Acute phase reactants: high-sensitivity C-reactive protein (hsCRP) The fraction of subjects whose ACR core measures of (1) and (2) decreased by ≥20%, ≥50%, or ≥70%, respectively, AND whose ACR core measures of at least 3 of (3)-(7) improved by≥20%, ≥50%, or ≥70%, respectively
DAS28-CRP	Disease activity evaluation score calculated with the formula below using TJC and SJC in 28 joints, PtGA on a 0-100 mmVAS, and hsCRP as factors: DAS28-CRP = $0.56\sqrt{\text{TJC}} + 0.28\sqrt{\text{SJC}} + 0.36\{\ln(\text{CRP} + 1)\} + 0.014 \times \text{PtGA} + 0.96$ Defined as follows: DAS28 >5.1, high disease activity; 3.2< DAS28 ≤5.1, moderate disease activity; 2.6≤ DAS28 ≤3.2, low disease activity; DAS28 <2.6, remission
HAQ-DI	Questionnaires on 8 sections related to activities of daily living of patients with RA (dressing/grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities). Assessment score on functioning status calculated (mean of the scores of the categories) by patient's self-assessment, scored on a 0-3 scale
mTSS	A scoring system for the extent of bone erosion in 44 joints and the extent of joint-space narrowing in 42 joints in the radiographs of the hands/wrists and feet. Scores are summed to evaluate the structural damage to the joints, with higher scores representing progression of joint destruction.
CDAI	Clinical disease activity score calculated with the formula below using TJC and SJC in 28 joints, and PtGA and PhGA on a 0-100 mmVAS as factors: CDAI = TJC + SJC + PtGA + PhGA Defined as follows: CDAI >22, high disease activity; 10< CDAI ≤22, moderate disease activity; 2.8< CDAI ≤10, low disease activity; CDAI ≤2.8, remission
ACR/EULAR Boolean Remission	A status that satisfies all of the following: TJC ≤1 (28 joints); SJC ≤1 (28 joints); hsCRP ≤1 mg/dL; PtGA ≤10 mm

VAS, Visual analog scale

The definition of each grade for abnormal laboratory test values is shown below.

	High cholesterol	High triglycerides	CPK increased	White blood cell count decreased
Grade 1	ULN-300 mg/dL	150-300 mg/dL	1-2.5 × ULN	3 × 10^3/μL-LLN
Grade 2	300-400 mg/dL	300-500 mg/dL	2.5-5 × ULN	2-3 × 10^3/μL
Grade 3	400-500 mg/dL	500-1,000 mg/dL	5-10 × ULN	1-2 × 10^3/μL
Grade 4	>500 mg/dL	>1,000 mg/dL	>10 × ULN	<1 × 10^3/μL
	Neutrophil count decreased	Lymphocyte count decreased	Haemoglobin decreased	Platelet count decreased
Grade 1	1.5 × 10^3/μL-LLN	0.8 × 10^3/μL-LLN	10 g/dL-LLN	75 × 10^3/μL-LLN
Grade 2	1-1.5 × 10^3/μL	0.5-0.8 × 10^3/μL	8-10 g/dL	50-75 × 10^3/μL
Grade 3	0.5-1 × 10^3/μL	0.2 × 0.5 × 10^3/μL	<8 g/dL	25-50 × 10^3/μL
Grade 4	<0.5 × 10^3/μL	<0.2 × 10^3/μL	Life-threatening	<25 × 10^3/μL
	Creatinine increased	Decreased serum phosphorus level	LLN, lower limit of normal ULN, upper limit of normal BL, baseline High/increased parameters: the upper bound is inclusive and the lower bound is exclusive. Low/decreased parameters: the lower bound is inclusive and the upper bound is exclusive	
Grade 1	1-1.5 × ULN/BL	2.5 mg/dL-LLN		
Grade 2	1.5-3 × ULN/BL	2.0-2.5 mg/dL		
Grade 3	3-6 × ULN/BL	1.0-2.0 mg/dL		
Grade 4	>6 × ULN	<1.0 mg/dL		

Review Report (2)

August 26, 2020

Product Submitted for Approval

Brand Name	Jyseleca Tablets 100 mg Jyseleca Tablets 200 mg
Non-proprietary Name	Filgotinib Maleate
Applicant	Gilead Sciences K.K.
Date of Application	October 8, 2019

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, clinical positioning, indication, and dosage and administration

At the Expert Discussion, the expert advisors largely supported the PMDA's conclusions on the efficacy, clinical positioning, indication, and dosage and administration presented in Review Report (1). The following comments were made by the expert advisors:

- As for the dose adjustment for patients with renal impairment, it is appropriate to specify a dosage regimen of 100 mg once daily for patients with moderate renal impairment. While it is possible to specify a dosage regimen of 100 mg once daily for patients with severe renal impairment, given that many patients in Japan are of low body weight, filgotinib is not positively recommended for this patient group.

PMDA's view:

In Study GLPG0634-CL-106 [see Section 6.2.2.2], FILGOTINIB 100 mg was administered once daily to 3 subjects with severe renal impairment, and in Study GLPG0634-CL-110 [see Section 6.2.1.1], FILGOTINIB 200 mg was administered once daily to 6 healthy subjects. Table 81 shows exposures of filgotinib and GS-829845 at steady state. Comparisons among studies indicated that the exposures of filgotinib in the subjects with severe renal impairment were lower than those in healthy subjects, with similar exposures of GS-829845. The exposures of filgotinib and GS-829845 in the patients with severe renal impairment did not tend to be higher than the exposures in patients with RA following filgotinib maleate 200 mg once daily estimated by population pharmacokinetic analysis (AUC_{tau}; filgotinib, 4.56 μg·h/mL; GS-829845, 75.1 μg·h/mL; Table 41).

Given that no adverse events were reported in subjects with severe renal impairment in Study GLPG0634-CL-106, it was concluded that no safety concerns have been raised at present that would make the filgotinib 100 mg once-daily regimen unacceptable for patients with severe renal impairment.

Table 81. Exposures of filgotinib and GS-829845 after multiple oral doses of FILGOTINIB ($AUC_{0\text{-}24h}$; μg·h/mL)

	GLPG0634-CL-106	GLPG0634-CL-110
n	3	6
Severity of renal impairment	Severe	Normal
Dosage regimen	100 mg once daily	200 mg once daily
Filgotinib	2.64 ± 0.90	5.58 ± 1.19
GS-829845	66.6 ± 12.3	62.1 ± 16.8

Mean ± standard deviation

However, there were a limited number of subjects with severe renal impairment analyzed in Study GLPG0634-CL-106, and there is a certain degree of correlation between the severity of renal impairment and the exposure of filgotinib and GS-829845. Given that there were trends towards increase in the risk of dose-dependent occurrence of some of the adverse events or fluctuation in laboratory values in the study in patients with RA [see Section 7.R.5.1], the appropriateness of the use of filgotinib in patient with severe renal impairment should be decided carefully, and the patient should be closely monitored during filgotinib treatment for any sign of adverse reactions.

On the basis of the above, PMDA requested the applicant to include a precaution for use in patients with severe renal impairment in the package insert, and the applicant agreed to take such action.

1.2 Safety, post-marketing investigations, and risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusions on the safety and post-marketing investigations presented in Review Report (1). The following comments were made by the expert advisors:

- Since decreases in serum phosphorus levels have rarely been reported in association with other JAK inhibitors, the events are unique to filgotinib. Hypophosphataemia may be unnoticed unless strongly suspected by the physician, and therefore it is important to measure serum phosphorus levels on a regular basis.
- Given the results from non-clinical and clinical studies, there is little need to require the use of contraception in male patients who have received filgotinib; however, before administering filgotinib to male patients with reproductive potential, they should be cautioned about the risk of reduced fertility accompanied by impaired spermatogenesis associated with filgotinib treatment.

On the basis of the discussion at the Expert Discussion, PMDA concluded that it is necessary to include caution statement regarding the risk of reduced fertility accompanied by impaired spermatogenesis associated with filgotinib treatment before starting filgotinib treatment in male patients with reproductive potential, and to provide information about the incidence of decreased serum phosphorus levels reported in the clinical studies. The risk of hypophosphataemia should be properly evaluated through the measurement of serum phosphorus levels on a regular basis in the planned specified use-results survey covering all patients who will be receiving

filgotinib, and the need for additional safety measures including periodic measurement of serum phosphorus levels should be decided based on the obtained data.

On the basis of the above, PMDA requested the applicant to provide caution statement and information in the package insert, and risk evaluation for hypophosphataemia should be performed. The applicant agreed to take such action.

In view of the discussion in Section "7.R.6 Post-marketing safety measures" in Review Report (1) and discussion at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for filgotinib should include the safety specification presented in Table 82, and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 83. PMDA requested the applicant to conduct post-marketing surveillance and investigate the issues above.

Table 82. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious infection (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, opportunistic infection) • Herpes zoster • Venous thromboembolism • Gastrointestinal perforation • Liver disorder • Interstitial lung disease • Neutrophil count decreased, lymphocyte count decreased, haemoglobin decreased • Reactivation of hepatitis B virus	• Reduction in male fertility accompanied by impaired spermatogenesis • Malignancy • Cardiovascular events • Rhabdomyolysis, myopathy • Hypophosphataemia	None
Efficacy specification		
None		

Table 83. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance) • Post-marketing clinical study[a)]	None	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate information regarding the proper use of filgotinib to healthcare professionals • Organize and disseminate brochures for patients and their families • Ensure that information on the proper use is provided before the delivery of the product.

a) The FINCH4 study will be switched to post-marketing clinical study after approval of filgotinib

The applicant's explanation:

As shown in Table 84, a specified use-results survey will be conducted covering all patients who will be receiving filgotinib during a 3-year observation period. The survey will continue until data from a specified number of patients with RA who had an inadequate response to conventional therapies are accumulated (planned sample size, 1,000) to investigate the safety and efficacy of filgotinib in clinical use. The incidence

of malignancy and death will be followed for up for 3 years regardless of whether filgotinib treatment is continued for the entire period to further investigate the safety in long-term treatment.

Table 84. Outline of specified use-results survey (draft)

Objective	To collect and assess data on the long-term safety and efficacy of filgotinib in clinical use
Survey method	Central registration system (all-case surveillance)
Population	Patients with RA who had inadequate response to conventional therapies
Observation period	3 years
Planned sample size	1,000 patients (as safety analysis population)
Main survey items	• Safety specification: Important identified risks and important potential risks presented in Table 82 (except for reduction in male fertility accompanied by impaired spermatogenesis) • Patient characteristics (e.g., body weight, age, severity, disease duration, prior medical history, complications, degree of renal impairment) • Treatment status with filgotinib • Prior RA treatment • Coadministered drugs/therapies • Laboratory values • Adverse events • Efficacy evaluation

PMDA accepted the applicant's actions. Gathered information should be publicly announced via information materials and the applicant's website so that necessary information will be provided to healthcare professionals without delay.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following approval conditions. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. Both the drug product and its drug substance are classified as powerful drugs.

Indication

Rheumatoid arthritis <u>in patients who have had an inadequate response to conventional therapies</u> (including the prevention of structural joint damage)

(The underlined denotes addition to the proposed indication.)

Dosage and Administration

The usual adult dosage is 200 mg of filgotinib orally once daily. The dose may be adjusted to 100 mg once daily according to the patient's condition.

(No change made to the proposed Dosage and Administration.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specific number of patients have been collected, in order to promptly collect

data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

Appendix

List of Abbreviations

ACR	American College of Rheumatology
ACR20/50/70 improvement response	American College of Rheumatology 20%, 50%, or 70% improvement
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	AUC from time zero to time t
AUC_{tau}	AUC during a dosing interval
AUC_{inf}	AUC from time zero to infinity
AUC_{last}	AUC to last measured time point
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
CCP	Cyclic citrullinated peptide
CDAI	Clinical disease activity index
cDMARDs	Conventional disease modifying anti-rheumatic drugs
CES	Carboxylesterase
CI	Confidence interval
CIA	Collagen-induced arthritis
CHO	Chinese hamster ovary
CL	Clearance
CL_{cr}	Creatinine clearance
CL/F	Apparent clearance
CL_R	Renal clearance
C_{max}	Maximum observed concentration
CPCA	Cyclopropanecarboxylic acid
CPK	Creatine phosphokinase
CRP	C-reactive protein
C_{tau}	Concentration during a dosing
eGFR	Estimate glomerular filtration rate
FAS	Full analysis set
FSH	Follicle stimulating hormone
GALT	Gut-associated lymphoid tissue
GC	Gas chromatography
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEK	Human embryonic kidney
hERG	Human ether-a-go-go related gene
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
IFN	Interferon
IL	Interleukin
IR	Infrared absorption spectroscopy
JAK	Janus kinase
JP	Japanese Pharmacopoeia

JCR RA Treatment Guidelines 2014	Guidelines for the Management of Rheumatoid Arthritis, issued by Japan College of Rheumatology 2014
Jyseleca	Jyseleca Tablets 100 mg, Jyseleca Tablets 200 mg (Filgotinib maleate)
k_a	First-order absorption rate constant
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LH	Luteinizing hormone
LLN	Lower limit of normal
MACE	Major adverse cardiovascular events
MATE	Multidrug and toxin extrusion
MC	Methylcellulose
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MMRM	Mixed-effects model for repeated measures
MTX	Methotrexate
NMR	Nuclear magnetic resonance spectroscopy
NMSC	Non-melanoma skin cancer
NRI	Nonresponder imputation
NRU	Neutral red uptake
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
Peficitinib	Peficitinib hydrobromide
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PTP	Press through packaging
QbD	Quality by Design
QTc	Corrected QT interval
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RH	Relative humidity
SOC	System organ class
STAT	Signal transducer and activator of transcription
t_{max}	Time to maximum observed concentration
TNF	Tumor necrosis factor
Tofacitinib	Tofacitinib citrate
TR-FRET	Time-resolved fluorescence response energy transfer
TYK2	Tyrosine kinase 2
$t_{1/2}$	Elimination half-life
T2T	Treat to target
ULN	Upper limit of normal
Upadacitinib	Upadacitinib hydrate
UV-VIS	Ultraviolet-visible spectroscopy
V_c/F	Apparent central volume of distribution
V_{ss}	Volume of distribution at steady state