



# Filgotinib: A Clinical Pharmacology Review

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## Abstract

Filgotinib (GS-6034, formerly GLPG0634; Jyseleca<sup>®</sup>) is an oral, preferential Janus kinase (JAK)-1 inhibitor. Preferential inhibition of JAK1 modulates a subset of proinflammatory cytokines within the JAK–signal transducer and activator of transcription pathway, which differ from those inhibited by JAK2 or JAK3. Filgotinib is absorbed extensively and rapidly after oral dosing and is metabolized by carboxylesterase isoform 2 to form its primary active metabolite, GS-829845. The primary metabolite has a similar JAK1 selectivity profile but reduced activity (by 10-fold) and increased systemic exposure (approximately 16- to 20-fold) compared with the parent compound. Both the parent and the metabolite demonstrate low binding to plasma proteins in humans (<60%). Systemic exposures of filgotinib and its primary metabolite increase dose proportionally over a 50- to 200-mg once-daily dose range. Food does not affect the pharmacokinetics of filgotinib. Consistent with their terminal elimination half-lives (4.9–10.7 h for filgotinib and 19.6–27.3 h for the primary metabolite), steady state in plasma is reached by day 2 for filgotinib and day 4 for its metabolite. Filgotinib is mainly eliminated in the urine as the metabolite (>80%). Intrinsic factors such as age, sex, race, mild renal impairment, and mild-to-moderate hepatic impairment have either no or minimal impact on the pharmacokinetics of filgotinib and its primary metabolite. Filgotinib has a low drug–drug interaction potential, without clinically significant interactions with commonly coadministered medications in patients with inflammatory diseases. Both filgotinib and its primary metabolite are substrates of P-glycoprotein (P-gp); however, coadministration with P-gp inhibitors and inducers does not affect filgotinib pharmacokinetics sufficiently to warrant dose adjustment. Neither filgotinib nor its primary metabolite affect the corrected QT interval (calculated using Fridericia's correction formula). Filgotinib is approved for the treatment of rheumatoid arthritis and ulcerative colitis in Europe, the UK, and Japan.

## 1 Introduction

The Janus kinase (JAK)-signal transducer and activator of transcription (JAK-STAT) pathway is a key driver of rheumatoid arthritis (RA), Crohn's disease (CD), and ulcerative colitis (UC) by way of mediating the response to multiple proinflammatory cytokines and cellular growth factors [1–4]. Inhibition of the JAK-STAT pathway has demonstrated efficacy in immune-mediated diseases and has been identified as a novel therapeutic target for the treatment of RA [5], CD, and UC [6, 7]. Preferential inhibition of JAK1

### Key Points

Following oral dosing, filgotinib is rapidly converted to its primary active metabolite, which has a similar Janus kinase 1 selectivity profile and contributes to the overall pharmacodynamic response.

Filgotinib has a low drug–drug interaction potential without clinically significant interactions with commonly coadministered medications, such as methotrexate or statins; cytochrome P450 3A4 substrates, including oral contraceptives; and acid-reducing agents, including proton pump inhibitors and histamine antagonists.

Intrinsic factors such as age, sex, race, mild renal impairment, and mild-to-moderate hepatic impairment have either no or minimal impact on the pharmacokinetics of filgotinib and its primary metabolite.

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modulates a subset of proinflammatory cytokines within the JAK-STAT pathway that differ from those inhibited by JAK2 or JAK3 and that could improve the benefit–risk profile in comparison with that of pan-JAK inhibitors [8, 9]. Filgotinib is a second-generation preferential JAK1 inhibitor. In biochemical assays, filgotinib preferentially inhibited the activity of JAK1 and showed >5-fold higher potency for JAK1 over JAK2, JAK3, and tyrosine kinase 2 [10, 11]. Filgotinib has an active primary metabolite—GS-829845 (previously G254445)—which has a similar JAK1 selectivity profile but 10-fold lower potency in human whole blood assay than the parent compound [12]. In humans, exposure to this primary metabolite is 16- to 20-fold higher than to the parent filgotinib [13]. Filgotinib exposure following 200 mg once-daily (QD) dosing covers the half-maximal inhibitory concentration (IC<sub>50</sub>) for JAK1 in human whole blood [13].

Filgotinib is approved for the treatment of RA in Europe, the UK, and Japan but has not received approval for any indication in the USA. Clinical trials have shown that filgotinib has an onset of action as early as week 2, sustained efficacy, and a proven safety profile in patients with moderate-to-severe RA who have had an inadequate response to methotrexate, are biologic naïve, or are biologic experienced [14, 15]. Filgotinib has also demonstrated efficacy and safety in combination with methotrexate in a phase III study in patients with active RA who had limited or no prior exposure to methotrexate [16]. Filgotinib is approved for the treatment of UC in Europe, the UK, and Japan, having demonstrated early symptomatic relief and sustained efficacy in a phase III trial in patients with UC who were biologic naïve or biologic experienced [17]. Filgotinib also displayed a promising clinical profile in a phase II study in patients with CD, inducing clinical remission in significantly more patients compared with placebo [7].

## 2 Basic Properties of Filgotinib

### 2.1 Physicochemical Features

Filgotinib [*N*-(5-(4-((1,1-dioxidothiomorpholin-4-yl)methyl)phenyl)[1,2,4]triazole[1,5- $\alpha$ ]pyridin-2-yl)cyclopropanecarboxamide(2*Z*)but-2-enedioate] is an orally bioavailable JAK inhibitor (Fig. 1). It is categorized as a class II drug according to the Biopharmaceutics Classification System, based on its high permeability and low solubility [18]. A study in human epithelial colorectal adenocarcinoma (Caco-2) cell monolayers showed an apparent permeability of  $3.5 \times 10^{-6}$  cm/s, with an efflux ratio of 16.0. This was

lower than that of the high-permeability reference substance, propranolol (permeability  $22.7 \times 10^{-6}$  cm/s) [19]. However, following oral administration of 100 mg [<sup>14</sup>C]-filgotinib in a mass balance study, 87% of radioactivity was excreted in the urine, indicating that filgotinib permeability is high, with near complete absorption [10]. In healthy subject studies, filgotinib was rapidly absorbed after single and repeated oral administration [13].

### 2.2 Analytical Methods

Plasma concentrations of filgotinib and its primary metabolite were determined simultaneously using a validated liquid chromatography–tandem mass spectrometry assay [13, 20, 21]. JAK1 inhibition was investigated using fluorescence-activated cell-sorting analysis on blood samples, by measuring STAT1 phosphorylation (pSTAT1) in interleukin-6-stimulated blood [22]. Similarly, JAK2 inhibition was investigated by measuring STAT5 phosphorylation (pSTAT5) to confirm selectivity *in vivo*.

## 3 Human Pharmacokinetics

### 3.1 Absorption and Bioavailability

Filgotinib was rapidly absorbed following oral administration in healthy subjects, with maximum (peak) plasma concentrations ( $C_{\max}$ ) reached within 1 to 3 h postdose (Table 1). Filgotinib exposure (both  $C_{\max}$  and area under the plasma concentration–time curve [AUC]) increased dose proportionally over the dose range of 50 to 200 mg. Overall, inter-subject variability of AUC and  $C_{\max}$  at steady state was low to moderate (inter-subject coefficient of variation [CV%] range 16–44%) [13]. With regards to the primary metabolite, plasma concentrations were detected within 30 min after single doses and reached a maximum 3 to 8 h postdose (Table 1). As with the parent compound,  $C_{\max}$  and AUC increased dose proportionally within the 50 to 200 mg dose range. Inter-subject variability of AUC and  $C_{\max}$  of the metabolite at steady state was low (inter-subject CV% <26%). Primary metabolite exposures were on average 16- to 20-fold higher than filgotinib exposures [13].

Various formulations have been used throughout the clinical development of filgotinib, all of which have demonstrated similar exposures, including the drug product used in the phase IIb studies (a hydrochloride trihydrate salt) and the maleate salt tablet formulation selected for use in the phase III studies and subsequently commercialized (Fig. 2) [10, 21].

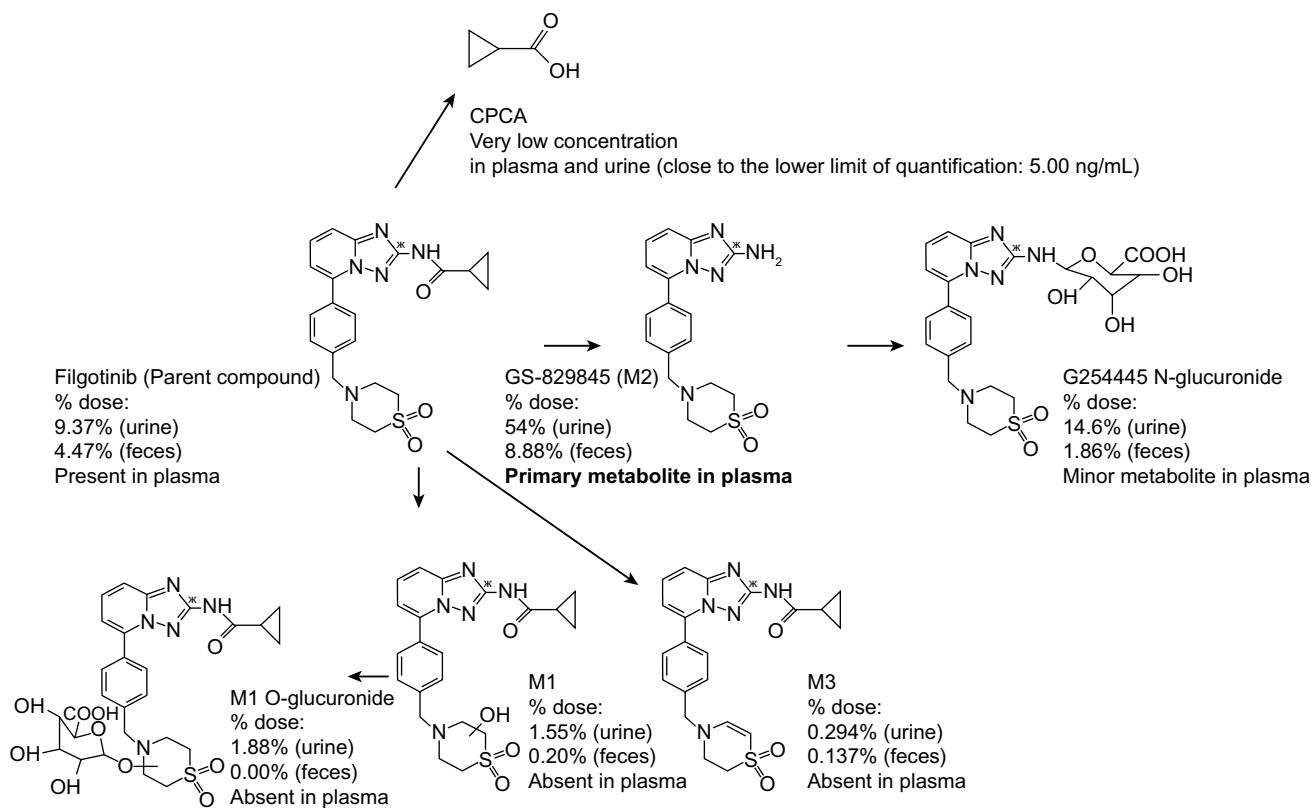


Fig. 1 Human metabolic pathway of filgotinib (data on file). CPCA cyclopropanecarboxylic acid

### 3.2 Effect of Food

Filgotinib can be administered without regard to food intake, as demonstrated in an evaluation of the commercialized maleate salt tablet formulation. Effects of both a high-fat (approximately 800 calories with 50% from fat) and a low-fat (approximately 400 calories with 20% from fat) meal on the pharmacokinetics of a single 200 mg dose of filgotinib were compared with those of fasting conditions in healthy subjects [21]. Slight decreases were noted for filgotinib  $C_{max}$ , with both the high-fat (20%) and the low-fat (11%) meal versus fasting (Fig. 3a). Food intake delayed absorption of

filgotinib, with a median time to reach  $C_{max}$  following drug administration ( $t_{max}$ ) of 1 h while fasting, which increased to 2 h with a low-fat meal and to 3 h with a high-fat meal. These effects were marginal and not considered clinically relevant. Neither the high-fat nor the low-fat meal affected the pharmacokinetics of the primary metabolite (Fig. 3b) [21]. This lack of effect was consistent with the high solubility of the maleate salt formulation in simulated intestinal fluids (data on file). Based on results from this study, the filgotinib tablet formulation was administered without regard to food in phase III studies.

Table 1 Pharmacokinetics of filgotinib and its primary metabolite after a single oral dose of filgotinib in healthy subjects [13]

Filgotinib dose	Filgotinib				Primary metabolite			
	$C_{max}$ , µg/mL	$t_{max}$ , h	$AUC_{\infty}$ , µg·h/mL	$t_{1/2}$ , h	$C_{max}$ , µg/mL	$t_{max}$ , h	$AUC_{\infty}$ , µg·h/mL	$t_{1/2}$ , h
100 mg (n=6)	0.57 (33.9)	2.00 (0.500–3.00)	1.74 (14.3) <sup>a</sup>	4.91 (11.5) <sup>a</sup>	0.96 (10.0)	5.00 (5.00–5.00)	30.2 (17.2)	22.5 (13.0)
200 mg (n=6)	1.16 (24.3)	3.00 (1.00–3.00)	4.84 (12.3) <sup>a</sup>	5.68 (39.6) <sup>a</sup>	2.29 (18.7)	5.00 (3.00–8.00)	63.8 (22.2)	20.0 (19.6)

Estimates are arithmetic means (CV%) except median (range) for  $t_{max}$

$AUC_{\infty}$  area under the plasma concentration–time curve from time zero to infinity,  $C_{max}$  maximum (peak) plasma concentration, CV coefficient of variation,  $t_{1/2}$  apparent terminal half-life,  $t_{max}$  time to reach  $C_{max}$  following drug administration

<sup>a</sup>n = 4

### 3.3 Distribution and Protein Binding

Binding of filgotinib or its primary metabolite to plasma proteins was determined in vitro by equilibrium dialysis using [ $^{14}\text{C}$ ]-filgotinib or cold compound. Protein binding of filgotinib was low in all evaluated species, with a value of 55–59% in humans and 32–70% in animal species. Binding of the primary metabolite to plasma proteins was similar to that of filgotinib, with values of 39–44% in humans and 29–55% in animal species [10] (data on file). After oral administration of [ $^{14}\text{C}$ ]-filgotinib to healthy male subjects, geometric mean whole blood-to-plasma total radioactivity ratios fluctuated between 0.9 and 1.1, suggesting some affinity of the radioactivity for red blood cell elements [10]. Protein binding of filgotinib and its primary metabolite were unchanged in patients with moderate hepatic impairment compared with healthy controls (bound fraction 56–59% and 39–45%, respectively) [23].

Data from two studies in healthy subjects and a proof-of-concept study in patients with RA were used to develop estimates for several filgotinib pharmacokinetic parameters. The apparent volume of distribution of filgotinib was 3.1 L (95% confidence interval [CI] 2.2–3.6) in the central compartment and 4.7 L (95% CI 4.4–5.0) in the peripheral compartment. These findings were comparable to the apparent volume of distribution of the metabolite compartment (4.4 L [95% CI 4.3–4.4]) [13].

### 3.4 Metabolism

Carboxylesterases (CESs) are the enzymes responsible for the formation of the primary metabolite [24]. CESs belong to the serine hydrolase superfamily of enzymes, of

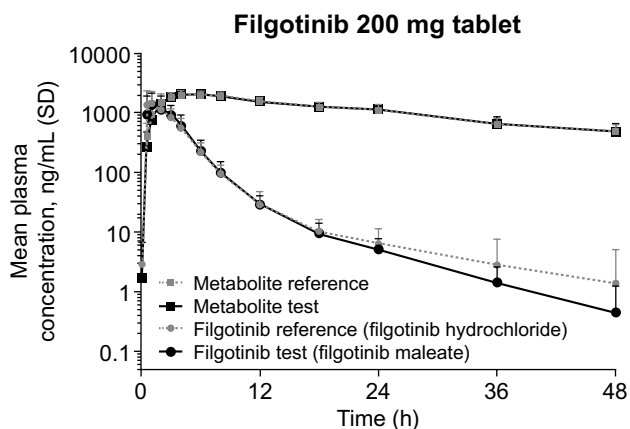
which there are six CES isoforms. The two most important forms of CESs for drug metabolism in humans are CES1 and CES2 [25]. Human CES2 is found mainly in the intestine and, to a lesser extent, in the liver, whereas CES1 is found mainly in the liver [25]. Following administration of 100 mg [ $^{14}\text{C}$ ]-filgotinib to healthy subjects, two metabolites were identified and quantified in plasma: the primary metabolite and its *N*-glucuronide derivative (Fig. 1). The primary metabolite accounted for approximately 92% of the total radioactivity in plasma, and both metabolites accounted for 68.6% of the total radioactivity in urine. Cleavage of filgotinib into its primary metabolite released cyclopropanecarboxylic acid (CPCA). CPCA was recorded at very low concentrations (close to the lower limit of quantification of 5.00 ng/mL) in plasma and urine but formed conjugates with endogenous amino acids, such as carnitine, taurine, and glycine [18]. Other minor filgotinib metabolites included M1 and M3 (accounting for 1.55% and 0.294% of the total radioactivity in urine, respectively) (Fig. 1).

### 3.5 Elimination

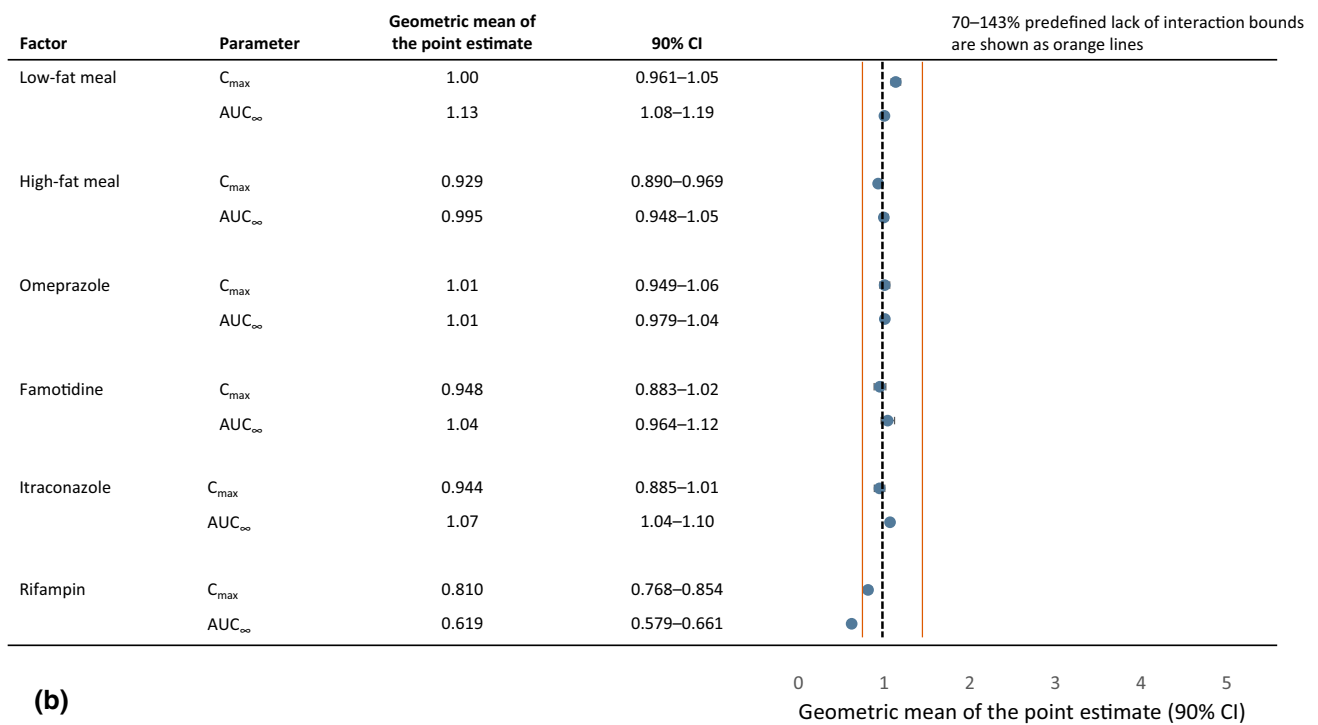
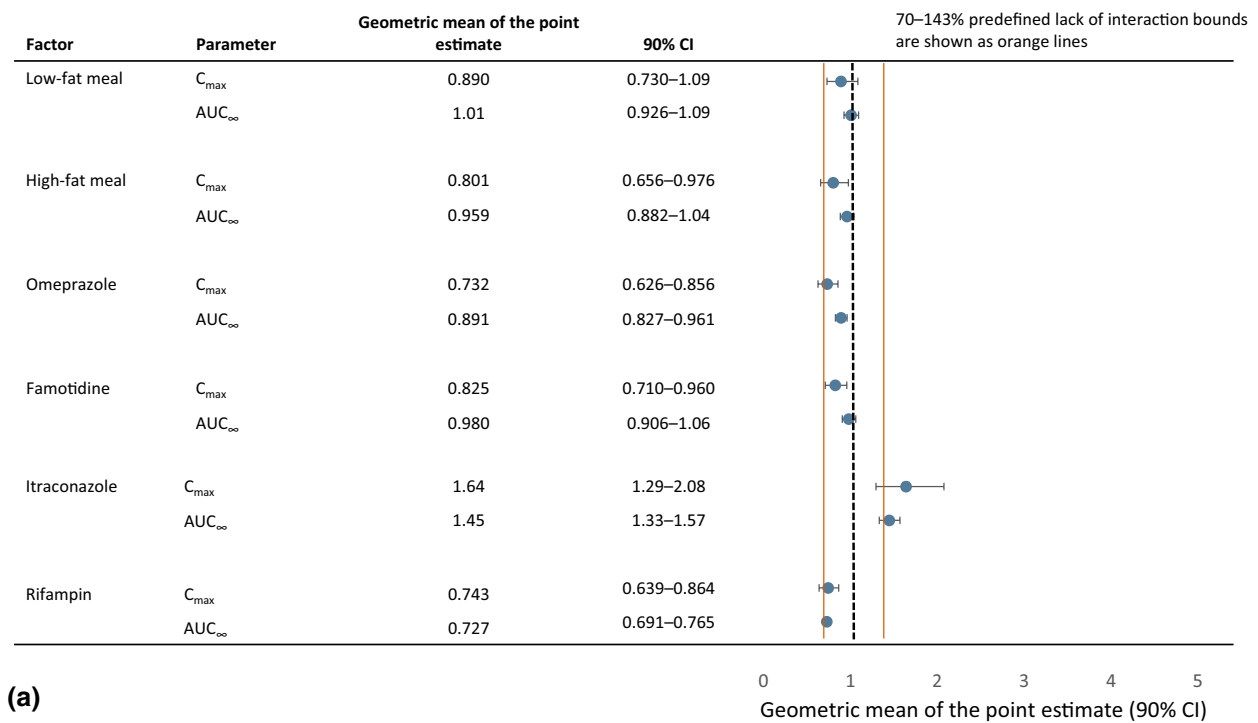
Following administration of [ $^{14}\text{C}$ ]-filgotinib 100 mg to healthy male subjects, 86.9% of the dose (filgotinib and its metabolites) was recovered from urine, which suggested that the majority of filgotinib and its metabolites were cleared by the kidneys [10]. Urinary excretion was rapid, with approximately half of recovery achieved within 24 h of dosing. Eight metabolites were identified in the urine and seven in the feces. Similar to observations involving plasma, the primary metabolite and its *N*-glucuronide derivative were the most prevalent, representing 54.0% and 14.6% of the total radioactivity in urine, and 8.9% and 1.9% of the total radioactivity in feces, respectively. Each of the remaining metabolites identified in the urine and feces represented, on average, less than 2.2% and 0.3% of the total radioactivity, respectively. The identical metabolite pattern in urine and feces suggested some biliary excretion of filgotinib and its metabolites (data on file).

### 3.6 Accumulation, Half-Life, and Steady-State Pharmacokinetics

For filgotinib, no accumulation to steady state was observed after QD dosing, consistent with its relatively short half-life of 4.9 to 10.7 h (Tables 1 and 2). Steady state was reached on day 2 of dosing. After repeated dosing with filgotinib, plasma elimination of the primary metabolite displayed a monophasic pattern, with mean apparent terminal elimination half-life ( $t_{1/2}$ ) ranging between 19.6 and 27.3 h (Tables 1 and 2). Consistent with the terminal half-life, steady-state levels of the metabolite were achieved within 4 days, with an average 2-fold accumulation of the metabolite after QD dosing [13, 26–28].

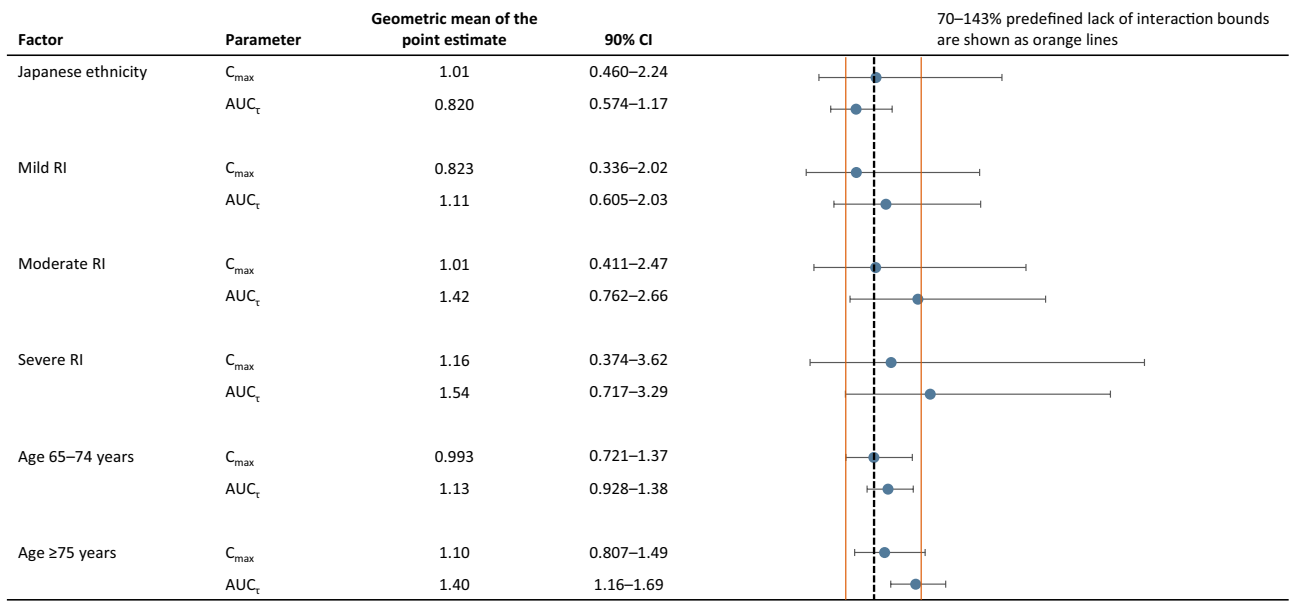


**Fig. 2** Mean  $\pm$  SD plasma concentrations of filgotinib and its primary metabolite following a single dose of filgotinib 200 mg maleate tablets (test) and filgotinib hydrochloride tablets (reference). SD standard deviation. Figure adapted from Anderson et al. [21] with permission from John Wiley and Sons. © 2019, The American College of Clinical Pharmacology



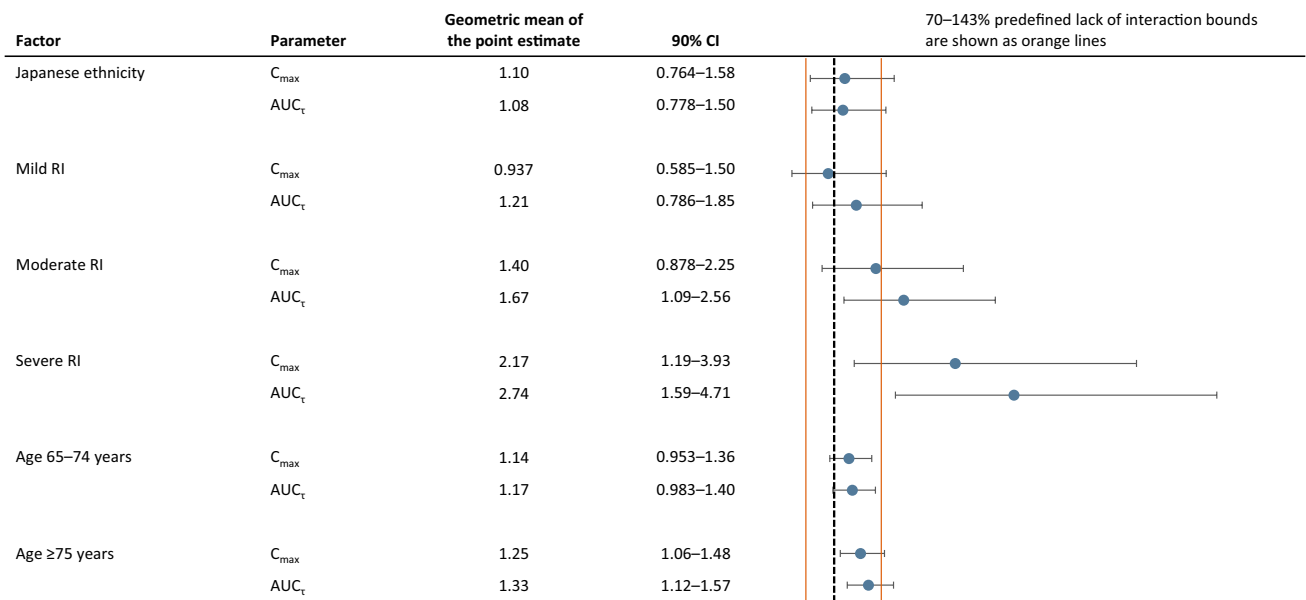
**Fig. 3** Effect of extrinsic factors on the pharmacokinetics of (a) filgotinib and (b) its primary metabolite; effect of intrinsic factors on the pharmacokinetics of (c) filgotinib and (d) its primary metabolite (geometric mean of the point estimate with 90% CIs). Geometric mean ratio for  $AUC_{\infty}$  is shown when filgotinib was given as a single dose; geometric mean ratio of  $AUC_{\tau}$  is shown when filgotinib was

given as multiple doses.  $AUC_{\infty}$  area under the plasma concentration–time curve from time zero to infinity,  $AUC_{\tau}$  area under the plasma concentration–time curve during a dosage interval ( $\tau$ ),  $CI$  confidence interval,  $C_{max}$  maximum (peak) plasma drug concentration,  $RI$  renal impairment



(c)

0 1 2 3 4 5  
Geometric mean of the point estimate (90% CI)



(d)

0 1 2 3 4 5  
Geometric mean of the point estimate (90% CI)

Fig. 3 (continued)

## 4 Effect of Intrinsic Factors on Filgotinib Pharmacokinetics

### 4.1 Age

Age had a limited impact on filgotinib exposure. In a dedicated study of filgotinib pharmacokinetics in healthy elderly subjects, no pharmacokinetic differences were noted

between subjects aged 65–74 years and those aged 40–50 years [26]. In subjects aged  $\geq 75$  years, filgotinib exposure ( $AUC$  during a dosage interval [ $AUC_{\tau}$ ]) was 1.4-fold higher than in those aged 40–50 years, but  $C_{max}$ ,  $t_{1/2}$ , and the amount of unchanged filgotinib excreted in urine were not altered. As with exposure to filgotinib, exposure ( $AUC_{\tau}$ ) to the primary metabolite was higher (by 1.3-fold) in subjects aged  $\geq 75$  years than in subjects aged 40–50 years after filgotinib



100 mg QD, with no change in the formation and elimination of the metabolite. This observation was supported by the constant metabolite-over-parent exposure ratio (from 18.4–19.4) over the entire age range. The relative differences in the pharmacokinetics of filgotinib and its primary metabolite between the two elderly age groups (65–75 and ≥ 75 years) are illustrated in Fig. 3c, d. Based on these data, it was concluded that age has no impact on the CESs involved in filgotinib metabolite formation [26]; however, because of a higher incidence of serious infections and limited clinical experience in patients with RA aged ≥ 75 years, caution is counselled when treating this population, and a starting filgotinib dose of 100 mg QD is recommended [10].

### 4.2 Japanese Ethnicity

The pharmacokinetics of filgotinib and its primary metabolite were compared between healthy Japanese and White subjects after 10 days of filgotinib 200 mg QD (Table 2; Fig. 3c, d) [29]. Filgotinib had a half-life of 6 h and 11 h in Japanese and White subjects, respectively, reaching steady-state plasma concentrations by day 2 in both populations. In Japanese and White subjects, the active metabolite reached higher plasma concentrations than filgotinib, consistent with its longer half-life (17–20 h). Overall exposures for filgotinib

and its metabolite were similar in both groups. These data indicate that the pharmacokinetic/pharmacodynamic profile of filgotinib is comparable in Japanese and White subjects [13].

### 4.3 Renal Impairment

Both filgotinib and its primary metabolite contribute to the overall clinical efficacy of the molecule; therefore, in instances where intrinsic/extrinsic factors show some effect on filgotinib or metabolite pharmacokinetics, both parent and metabolite exposures can be combined into a single parameter,  $AUC_{eff}$  (the sum of the AUC of filgotinib and its metabolite adjusted for their respective molecular weights and potencies), to more fully analyze whether dose adjustment is required [18]. Mild renal impairment (estimated glomerular filtration rate [eGFR] 60 to <90 mL/min/1.73 m<sup>2</sup>) had limited impact on filgotinib pharmacokinetics ( $AUC_{eff}$  increased by 1.5-fold); thus, no dose adjustment was required in these patients [10, 18]. By contrast, moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m<sup>2</sup>) increased  $AUC_{eff}$  by 2.0-fold, and severe renal impairment (eGFR 15 to <30 mL/min/1.73 m<sup>2</sup>) increased  $AUC_{eff}$  by 3.0-fold; as a result, a dose of filgotinib 100 mg QD is recommended

**Table 2** Pharmacokinetics of filgotinib and its primary metabolite after repeated oral doses of filgotinib 200 mg once daily

Source	Subjects	Filgotinib				Primary metabolite			
		$C_{max}$ , µg/mL	$t_{max}$ , h	$AUC_{\tau}$ , µg·h/mL	$t_{1/2}$ , h	$C_{max}$ , µg/mL	$t_{max}$ , h	$AUC_{\tau}$ , µg·h/mL	$t_{1/2}$ , h
Namour et al. [13]	Healthy subjects (n = 6)	1.20 (42.0)	2.00 (1.00–2.00)	4.45 (30.0)	5.17 (39.1) <sup>a</sup>	3.54 (21.2)	5.00 (3.00–5.00)	69.9 (25.6)	27.3 (7.81)
Namour et al. [29]	Japanese healthy subjects (n = 6)	3.77 (53.2)		6.08 (27.8)	6.35 (35.4)	5.09 (8.99)		81.4 (12.5)	16.7 (14.6)
Namour et al. [29]	White healthy subjects (n = 6)	3.06 (51.0)		5.58 (21.3)	10.7 (67.9)	3.87 (36.4)		62.1 (27.0)	19.6 (23.7)
SmPC [10]	RA (n = 37)	2.15 (48.1)		6.77 (43.7)		4.43 (29.3) <sup>b</sup>		83.2 (27.3) <sup>b</sup>	
SmPC [10]	UC (n = 13)	2.12 (50.3)		6.15 (28.1) <sup>c</sup>		4.02 (30.5)		72.1 (33.9) <sup>d</sup>	

Estimates are arithmetic means (CV%) except median (range) for  $t_{max}$ .

$AUC_{\infty}$  area under the plasma concentration–time curve from time zero to infinity,  $AUC_{\tau}$  area under the plasma concentration–time curve during a dosage interval ( $\tau$ ),  $C_{max}$  maximum (peak) plasma drug concentration,  $CV$  coefficient of variation,  $RA$  rheumatoid arthritis,  $SmPC$  summary of product characteristics,  $t_{1/2}$  apparent terminal half-life,  $t_{max}$  time to reach  $C_{max}$  following drug administration,  $UC$  ulcerative colitis

<sup>a</sup>n = 5

<sup>b</sup>n = 33

<sup>c</sup>n = 12

<sup>d</sup>n = 1

in patients with RA with moderate or severe renal impairment [10, 18]. As shown in Fig. 3c, d, the observed differences in exposures across patients with renal impairment of varying severity were more pronounced for the metabolite, consistent with its primary excretion route (at least 50% in urine) [29]. Filgotinib has not been studied in patients with end-stage renal disease (eGFR <15 mL/min/1.73 m<sup>2</sup>), so its use is therefore not recommended in this population [10].

#### 4.4 Hepatic Impairment

In a phase I study of patients with moderate hepatic impairment (Child–Pugh score B;  $n = 10$ ), AUC from time zero to infinity (AUC<sub>∞</sub>) for filgotinib and its primary metabolite increased by 1.6- and 1.2-fold, respectively, versus healthy controls ( $n = 10$ ), after a single dose of filgotinib 100 mg. Protein binding of filgotinib and its primary metabolite was unchanged (see Sect. 3.3). The absence of substantial differences in the pharmacokinetics of filgotinib and its primary metabolite was anticipated in individuals with mild-to-moderate hepatic impairment as filgotinib is metabolized by CES2, an enzyme located mainly in the intestine. Consequently, no dose adjustment of filgotinib is required in patients with mild-to-moderate hepatic impairment [10, 23]; however, filgotinib has not been studied in patients with severe hepatic impairment (Child–Pugh score C) so is not recommended for use in this population [10].

#### 4.5 Disease State

The steady-state pharmacokinetics of filgotinib and its primary metabolite after administration of filgotinib 200 mg QD were investigated using intensive pharmacokinetic analyses across phase III trials in patients with moderate-to-severe RA (FINCH 1–3; NCT02889796, NCT02873936, NCT02886728) [10] and in patients with UC in the SELECTION study (NCT02914522) [10] (Table 3). Summary pharmacokinetic parameters in patients with RA and UC were comparable to those reported for healthy subjects (Tables 1 and 2).

#### 4.6 Sex and Body Weight

Although sex and weight have not been formally evaluated for potential effects on filgotinib pharmacokinetics in dedicated studies, they do not appear to have a clinically relevant effect on the pharmacokinetics of filgotinib or its metabolite [10].

## 5 Effects of Other Drugs on Filgotinib

### 5.1 Carboxylesterase Inhibitors

Human CES2 enzymes are the main isoforms responsible for the formation of the primary metabolite of filgotinib; they are localized mainly to the intestine and, to a lesser extent, the liver [24, 30]. These enzymes of the  $\alpha/\beta$ -hydrolase family are abundant, with ubiquitous tissue-expression profiles. Filgotinib is also metabolized by CES1, which is predominantly expressed in the liver but to a lesser extent than by CES2 [10, 24]. In vitro inhibition of CES2 by medications including fenofibrate, carvedilol, diltiazem, and simvastatin has been demonstrated, although the clinical relevance of these interactions is currently unknown [10]. In vitro characterization indicates that, even when CES2 is fully saturated, filgotinib metabolism is not completely abrogated, as CES1 can also form the primary metabolite [24].

### 5.2 P-Glycoprotein Inhibitors and Inducers

Both filgotinib and its primary metabolite are substrates of the xenobiotic compound transporter P-glycoprotein (P-gp) [10]. The potential effect of the potent P-gp inhibitor itraconazole (200 mg single dose with 1 h pretreatment) on the pharmacokinetics of filgotinib (100 mg single dose) was evaluated in healthy subjects. Coadministration of filgotinib with itraconazole increased filgotinib AUC<sub>∞</sub> and C<sub>max</sub> by 45% and 64%, respectively but did not affect the AUC<sub>∞</sub> or C<sub>max</sub> of its primary metabolite (Fig. 3a, b). Itraconazole increased the combined AUC<sub>eff</sub> of filgotinib and its primary metabolite by 21%, so no dose adjustment of filgotinib was deemed necessary [31]. The effect of the P-gp inducer rifampin (600 mg QD) on the pharmacokinetics of filgotinib (200 mg single dose) in healthy subjects was also evaluated. With coadministration, filgotinib AUC<sub>∞</sub> and C<sub>max</sub> were reduced by 27% and 26%, respectively, and the primary metabolite AUC<sub>∞</sub> and C<sub>max</sub> were reduced by 38% and 19%, respectively (Fig. 3a, b) [31]. The combined AUC<sub>eff</sub> was reduced by 33%. Based on the combined AUC<sub>eff</sub> of filgotinib and its metabolite in the presence of these drugs, filgotinib dose adjustment was not deemed to be warranted with coadministration of P-gp inhibitors or inducers [10].

### 5.3 Acid-Reducing Agents

As patients with inflammatory diseases are likely to receive acid-reducing agents, such as histamine H<sub>2</sub> antagonists and proton pump inhibitors, potential drug interactions have been evaluated with representative medications in each of these classes [21]. Administration of filgotinib (100 mg single dose) with simultaneously dosed omeprazole 40 mg



(with 5-day pretreatment at 40 mg QD) or 2 h after famotidine 40 mg (with 4-day pretreatment at 40 mg twice daily [BID]) had no effect on the plasma exposure of filgotinib ( $AUC_{\infty}$ ) or its metabolite ( $AUC_{\infty}$  and  $C_{max}$ ) (Fig. 3a, b) [21]. Coadministration of omeprazole slightly reduced the  $C_{max}$  of filgotinib by 27% (Fig. 3a) [21]. The effects of acid-reducing agents on filgotinib pharmacokinetics are not considered clinically relevant, and filgotinib dose adjustment is not required when coadministering these agents [10].

## 6 Effects of Filgotinib on Other Drugs

Overall, filgotinib has a low drug–drug interaction potential [24]. In vitro, filgotinib and its primary metabolite at clinically relevant concentrations did not meaningfully interact with most cytochrome P450 (CYP) enzymes or uridine 5'-diphospho-glucuronosyltransferases and did not inhibit most key drug efflux transporters. One exception is organic cation transporter 2 (OCT2), which was inhibited by both filgotinib and its metabolite, with  $IC_{50}$  values at least 11-fold higher than the  $C_{max}$  values that filgotinib and its metabolite reached with 200 mg QD dosing [24]. In vitro studies indicated that filgotinib and its metabolite may inhibit organic anion transporting polypeptides (OATP)1B1 and OATP1B3; however, a study in healthy subjects given filgotinib 200 mg QD alongside OATP probe substrates (atorvastatin and pravastatin/rosuvastatin) indicated that no dose adaptation was required for statins or other OATP substrates with filgotinib coadministration (see Sect. 6.4) [32]. In vitro studies are inconclusive regarding the potential of filgotinib to induce CYP2B6 and induce or inhibit CYP1A2. Caution is therefore recommended when coadministering filgotinib with CYP1A2 substrates if the therapeutic index is narrow, such as is the case with warfarin [10]. In the presence of a probe substrate at concentrations of up to 200 and 500  $\mu$ M, maximum inhibition of P-gp was 3.0% and 0% with filgotinib and its primary metabolite, respectively ( $IC_{50}$  >200 and >285  $\mu$ M, respectively) [data on file]. At the same maximum concentrations, filgotinib and its primary metabolite inhibited the breast cancer resistance protein (BCRP) by 20.9% and 0%, respectively ( $IC_{50}$  >200 and >285  $\mu$ M, respectively) [data on file]. As such, filgotinib and its primary metabolite were deemed not to meaningfully inhibit P-gp or BCRP at clinically relevant concentrations. Overall, all in vitro and clinical data on drug-metabolizing enzymes and key drug transporters support coadministration of filgotinib with drugs commonly used for patients with inflammatory diseases without the need for dose adjustments.

### 6.1 Midazolam

To confirm and validate the in vitro results, the potential for interaction with CYP3A4 was investigated in healthy subjects using the sensitive CYP3A4 substrate midazolam (2 mg single dose) administered alone or after filgotinib 200 mg QD for 7 days. Neither the  $C_{max}$  nor the  $AUC_{\infty}$  of midazolam were affected by coadministration of filgotinib (Fig. 4). The point estimate pairwise comparisons for midazolam  $AUC_{\infty}$  and  $C_{max}$  when coadministered with filgotinib versus midazolam alone were 1.1 (90% CI 1.0–1.2) and 1.0 (90% CI 0.9–1.1), respectively, meaning that no specific recommendation was warranted for coadministration of filgotinib with CYP3A4 substrates [10, 24].

### 6.2 Hormonal Contraceptives

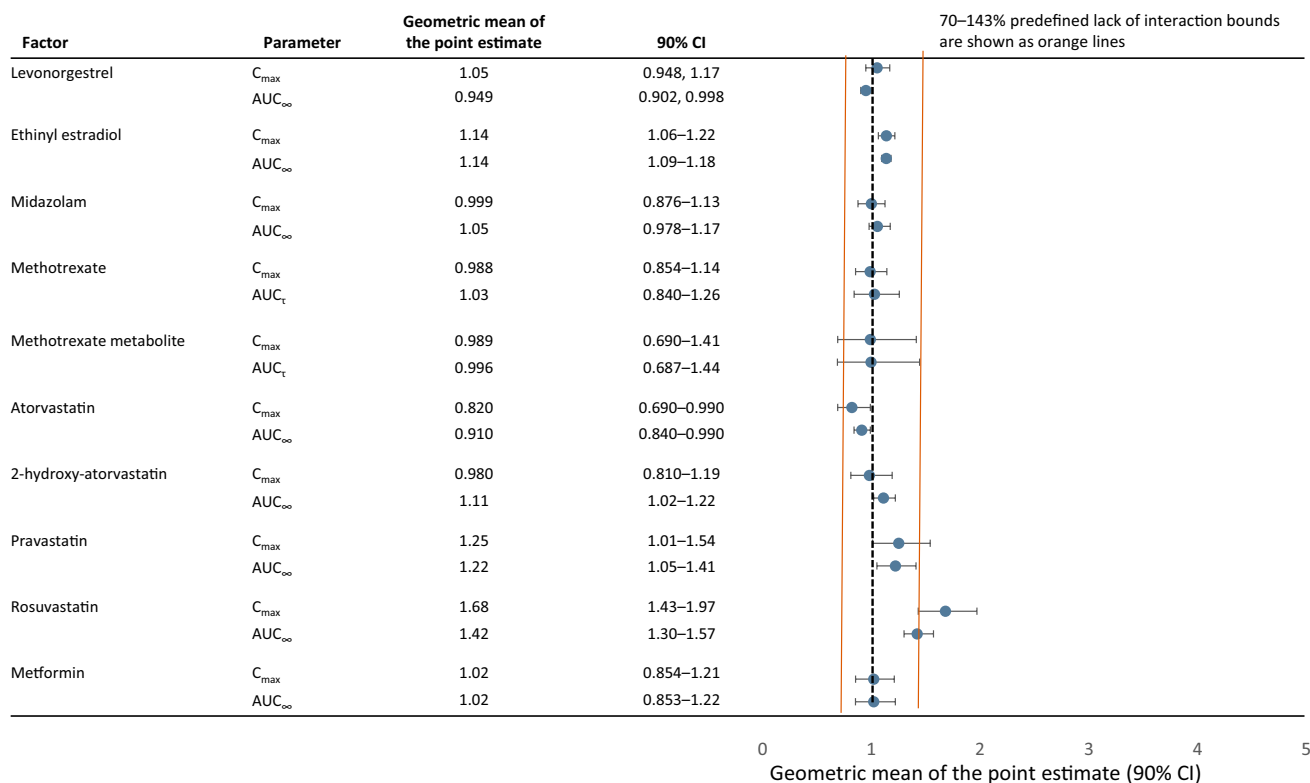
Since there may be mechanisms of enzyme induction/inhibition relevant to hormonal contraceptives that are presently poorly characterized (e.g., increased ethinyl estradiol due to sulfotransferase inhibition, which has been associated with thrombosis [33, 34]), the effects of filgotinib (200 mg QD for 15 days) on hormonal contraceptives (single doses of 30  $\mu$ g ethinyl estradiol/150  $\mu$ g levonorgestrel before and after filgotinib) were evaluated in healthy female subjects [35]. For both levonorgestrel and ethinyl estradiol, the percentage geometric least squares mean (GLSM) ratios and associated 90% CIs of  $C_{max}$  and  $AUC_{\infty}$  were contained within the prespecified lack of interaction bounds (70–143%) when coadministered with filgotinib (Fig. 4) [35]. Based on these results, no dose adjustment was warranted for coadministration of filgotinib with hormonal contraceptives [10, 35].

### 6.3 Metformin

The oral antidiabetic metformin is a substrate of OCT2 and of multidrug and toxin extrusion (MATE) transporter 1 (MATE1) and MATE2-K. As in vitro assessments indicated that filgotinib and its primary metabolite are OCT inhibitors (albeit at supratherapeutic concentrations) [24], potential drug interactions between metformin (850 mg single dose) and filgotinib 200 mg QD were assessed. Metformin percentage GLSM ratios and associated 90% CIs for  $AUC_{\infty}$  and  $C_{max}$  were not altered by coadministration of filgotinib (Fig. 4), meaning that filgotinib dose adjustment with concomitant use of metformin and other OCT2 and MATE transporter substrates was deemed unnecessary [31].

### 6.4 Statins

In vitro data indicated that filgotinib and its primary metabolite may be inhibitors of OATP1B1 and OATP1B3



**Fig. 4** Effects of filgotinib on the  $C_{max}$  and  $AUC_{last}$  of levonorgestrel, ethinyl estradiol, midazolam, methotrexate, atorvastatin, pravastatin, rosuvastatin, and metformin (geometric mean of the point estimate with 90% confidence intervals). Geometric mean ratio for  $AUC_{\infty}$  is shown when the victim drug was given as a single dose; geometric

mean ratio of  $AUC_{\tau}$  is shown when the victim drug was given as multiple doses.  $AUC_{\infty}$  area under the plasma concentration–time curve from time zero to infinity,  $AUC_{\tau}$  area under the plasma concentration–time curve during a dosage interval ( $\tau$ ),  $C_{max}$  maximum (peak) plasma drug concentration

at suprathreshold filgotinib concentrations [10]. A phase I study was conducted in healthy subjects given filgotinib 200 mg QD for 11 days alongside single doses of the OATP probe substrates atorvastatin (40 mg) and a combination of pravastatin (40 mg)/rosuvastatin (10 mg) [32]. Of note, rosuvastatin is both an OATP and a BCRP substrate, and the combination of rosuvastatin and pravastatin as probes permits simultaneous measurement of the activity of the drug transporters OATP and BCRP in the presence of filgotinib [32]. Although coadministration of filgotinib did not affect atorvastatin  $AUC_{\infty}$ , atorvastatin  $C_{max}$  was reduced by 18% (Fig. 4). Neither the  $AUC_{\infty}$  nor the  $C_{max}$  of the atorvastatin metabolite, 2-hydroxy-atorvastatin, were affected by coadministration with filgotinib (Fig. 4). Pravastatin  $AUC_{\infty}$  was unaffected by filgotinib; however, filgotinib increased pravastatin  $C_{max}$  by 25% and increased the  $C_{max}$  and  $AUC_{\infty}$  of rosuvastatin by 68% and 42%, respectively (Fig. 4). None of these changes were considered to represent a clinically meaningful effect of filgotinib coadministration on statin exposure, and no dose adjustment is required for statins or other OATP or BCRP substrates [32].

## 6.5 Methotrexate

Methotrexate is an OAT1 and OAT3 substrate that is a standard of care for the treatment of RA. The potential for drug interaction with filgotinib was assessed during a phase IIa study that investigated filgotinib in the treatment of patients with active RA and an inadequate response to methotrexate [24]. Patients received filgotinib 30, 75, 150, or 300 mg QD (or placebo) and continued their stable methotrexate dose (7.5–20 mg/kg weekly); pharmacokinetic data were pooled across filgotinib doses ( $n = 17$ ) because of the low patient numbers in individual dosing groups. The point estimate pairwise comparisons for methotrexate  $AUC_{\tau}$  and  $C_{max}$  when coadministered with filgotinib versus methotrexate alone fell within the lack of interaction bounds (70–143%; Fig. 4) [24]. These data indicate that filgotinib does not significantly impact the pharmacokinetics of methotrexate and support the coadministration of filgotinib with methotrexate without dose adjustment.

## 7 Thorough QTc Study

Filgotinib has no prolongation effect on the corrected QT interval (calculated using Fridericia's correction formula [QTcF] and an individual correction factor [QTcI]). A partially blinded, randomized, placebo- and positive-controlled (moxifloxacin 400 mg), four-period, multiple-dose, cross-over study was conducted to evaluate the effect of filgotinib (at doses of 200 and 450 mg QD for 7 days) on placebo-corrected QTcF ( $\Delta\Delta$ QTcF; primary endpoint) [20]. Plasma exposures of filgotinib and its primary metabolite were expectedly higher following administration of filgotinib 450 versus 200 mg QD (mean  $C_{\max}$  increase of 2.1- and 1.9-fold for filgotinib and its primary metabolite, respectively, over a 2.3-fold dose range). No QT prolongation occurred based on by-timepoint analysis. No clinically relevant relationships were observed between time-matched, baseline-adjusted, placebo-corrected QTc interval and plasma concentrations of filgotinib or its primary metabolite [20]. This represents a negative thorough QT study, as defined by International Conference on Harmonisation E14 guidance.

## 8 Pharmacokinetic–Pharmacodynamic Relationships

An analysis was performed based on early clinical data (studies in healthy subjects and a proof-of-concept study in patients with RA) to develop a preliminary population pharmacokinetic/pharmacodynamic model describing the time course of plasma concentrations of filgotinib and its primary active metabolite across the pharmacodynamic dose range of filgotinib (25–450 mg QD) [13]. The pharmacokinetics of filgotinib and its primary metabolite were adequately described by a combined two-compartment and a one-compartment model, respectively, with complete conversion of filgotinib into metabolite at all except the highest filgotinib doses. Individual status (healthy subject vs. patient with RA) and sex were included as statistically significant covariates on filgotinib and primary metabolite plasma clearance and on filgotinib intercompartmental clearance, respectively. Since the phase I studies included in the model were conducted exclusively in healthy male subjects and the proof-of-concept study included 33/36 (92%) female patients with RA, sex was confounded with study and subject status in this pharmacokinetic model. The relative inhibition of pSTAT1 in healthy subjects was described by a combined direct-response model of the predicted plasma concentration of filgotinib and its primary metabolite; drug effect on pSTAT1 inhibition was implemented as a sigmoidal maximum effect ( $E_{\max}$ ) model. No covariates were included in the model for

biomarker. Figure 5 shows the simulated steady-state inhibition of pSTAT1 for various filgotinib regimens [13].

The biomarker–response curve over the dosing interval correlated with the filgotinib and primary metabolite time profiles, suggesting that the prolonged metabolite exposure resulted in the maintenance of inhibition over the dosing interval, whereas the peak filgotinib exposure contributed to the maximal inhibition [13]. These data indicated that the maximum pharmacodynamic effect was achieved with a dose of filgotinib 200 mg QD and were used to support the dose and regimen selection for registration trials.

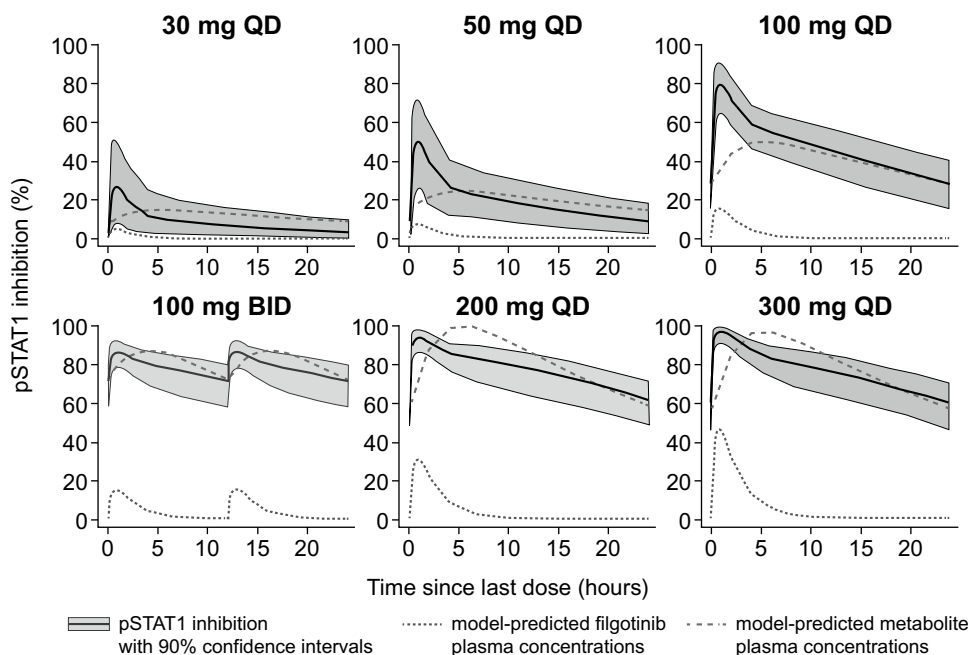
## 9 Summary/Conclusions

Filgotinib is a preferential JAK1 inhibitor that is metabolized to an active primary metabolite with similar JAK1 selectivity but with 10-fold lower potency and a relatively longer elimination half-life than the parent compound. Filgotinib 100 and 200 mg QD are approved for the treatment of RA in Europe and Japan. To date, filgotinib has been tested in various clinical studies in patients with RA [14–16, 36, 37], where doses of 100 to 200 mg QD or 50 to 100 mg BID were efficacious for signs and symptoms, with rapid-onset kinetics and a consistent safety profile. Of note, DARWIN 2 [36] examined filgotinib monotherapy, whereas the other listed trials included filgotinib in combination with methotrexate. Filgotinib 200 mg QD is approved for the treatment of UC in Europe and Japan and is being evaluated (dosed at 100 and 200 mg QD) for the treatment of CD in phase III trials (NCT02914561, NCT02914600).

Pharmacokinetic analysis following single and multiple ascending doses of filgotinib revealed rapid absorption following oral administration and conversion to its primary active metabolite. The pharmacokinetics of filgotinib and its metabolite were dose proportional over the dose range of 50 to 200 mg, with no notable food effect on the  $C_{\max}$  or  $AUC_{\infty}$ . As expected, based on its half-life of 4.9 to 10.7 h, filgotinib did not accumulate with QD or BID dosing. The metabolite has a longer half-life (19.6–27.3 h), reaching steady state within 4 days of chronic dosing and achieving a 2-fold accumulation in exposure after QD dosing. At steady state, exposures were approximately 16- to 20-fold higher for the primary metabolite than for the parent filgotinib [13].

Filgotinib pharmacokinetics appear to be similar between healthy subjects and patients with RA [10, 13] or UC [17], and intrinsic factors such as age, mild renal impairment, and mild-to-moderate hepatic impairment have either no or minimal impact on the pharmacokinetics of filgotinib and its primary metabolite [23, 26, 29]. Filgotinib has a low drug–drug interaction potential, without clinically

**Fig. 5** Simulated steady-state inhibition of pSTAT1 with 90% confidence intervals. The 90% confidence intervals shown represent parameter uncertainty and are based on 1000 replicates of the pharmacokinetic and pharmacokinetic/pharmacodynamic models describing STAT1 inhibition [13]. Gray dotted and gray dashed curves show model-predicted filgotinib and metabolite plasma concentrations, respectively (common arbitrary units). *BID* twice daily, *pSTAT* phosphorylated signal transducer and activator of transcription protein, *QD* once daily. Figure adapted from Namour et al. [13], distributed under the terms of a [Creative Commons Non-Commercial 4.0 International \(CC BY-NC 4.0\) license](https://creativecommons.org/licenses/by-nc/4.0/). © 2015, the author(s)



significant interactions with commonly administered comedications, including methotrexate; oral contraceptives and other CYP3A4 substrates; statins; and acid-reducing agents, such as proton pump inhibitors and histamine antagonists [21, 24, 31, 32, 35]. No dose adjustment is required when filgotinib is coadministered with other drugs [10, 24]. Both filgotinib and its primary metabolite are substrates of P-gp; however, coadministration with P-gp inhibitors or inducers does not affect filgotinib pharmacokinetics sufficiently to warrant dose adjustment [31]. Neither filgotinib nor its primary metabolite have shown an effect on QTcF interval [20].

In conclusion, the studies described herein support the use of filgotinib as a treatment for patients with RA and UC and potentially other inflammatory diseases, including CD, because of its pharmacokinetic/pharmacodynamic and efficacy profiles and acceptable tolerability [7, 14, 16, 17, 36].

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## Declarations

**Funding** Not applicable.

**Conflicts of interest** Florence Namour is an employee of Galapagos SASU. Kacey Anderson and Cara Nelson are former employees of Gilead Sciences, Inc., and hold stock in the company. Chantal Tasset is an employee of Galapagos NV.

**Ethics approval** Not applicable.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Availability of data and material** Data on file in this manuscript are not available for sharing per current Galapagos guidelines; other included data have been published previously as cited.

**Code availability** Not applicable.

**Authors' contributions** Florence Namour, Kacey Anderson, and Cara Nelson were involved in the manuscript conceptualization and design as well as the acquisition, analysis and interpretation of the study data discussed herein. Chantal Tasset provided project overview and interpretation of the study data discussed herein. All authors contributed to manuscript development and provided their approval to submit.

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## References

- Isomäki P, Junttila I, Vidqvist KL, Korpela M, Silvennoinen O. The activity of JAK-STAT pathways in rheumatoid arthritis: constitutive activation of STAT3 correlates with interleukin 6 levels. *Rheumatology (Oxford)*. 2015;54:1103–13. <https://doi.org/10.1093/rheumatology/keu430>.
- Neurath M. Current and emerging therapeutic targets for IBD. *Nat Rev Gastroenterol Hepatol*. 2017;14:688. <https://doi.org/10.1038/nrgastro.2017.138>.
- Schwartz DM, Bonelli M, Gadina M, O'Shea JJ. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat Rev Rheumatol*. 2016;12:25–36. <https://doi.org/10.1038/nrrheum.2015.167>.
- Walker JG, Smith MD. The Jak-STAT pathway in rheumatoid arthritis. *J Rheumatol*. 2005;32:1650–3.
- Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs*. 2017;77:521–46. <https://doi.org/10.1007/s40265-017-0701-9>.
- Olivera P, Danese S, Peyrin-Biroulet L. JAK inhibition in inflammatory bowel disease. *Expert Rev Clin Immunol*. 2017;13:693–703. <https://doi.org/10.1080/1744666X.2017.1291342>.
- Vermeire S, Schreiber S, Petryka R, Kuehbacher T, Hebuterne X, Roblin X, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. *Lancet*. 2017;389:266–75. [https://doi.org/10.1016/S0140-6736\(16\)32537-5](https://doi.org/10.1016/S0140-6736(16)32537-5).
- O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis*. 2013;72(Suppl 2):ii111–5. <https://doi.org/10.1136/annrheumdis-2012-202576>.
- Sandborn WJ, Feagan BG, De Hertogh G, Chen G, French DF, Huntzicker EG, et al. Filgotinib (GLPG0634, GS-6034), a JAK-1 selective inhibitor, significantly reduces gut tissue pSTAT3 in Crohn's disease patients. *Gastroenterology*. 2017;152(Suppl 1):S602.
- Gilead Sciences. Jyseleca summary of product characteristics. Available from: [https://www.ema.europa.eu/en/documents/product-information/jyseleca-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/jyseleca-epar-product-information_en.pdf). Accessed 9 Oct 2021.
- Traves PG, Murray B, Campigotto F, Galien R, Meng A, Di Paolo JA. JAK selectivity and the implications for clinical inhibition of pharmacodynamic cytokine signaling by filgotinib, upadacitinib, tofacitinib, and baricitinib. *Ann Rheum Dis*. 2021;80:865–75. <https://doi.org/10.1136/annrheumdis-2020-219012>.
- Galien R, Vayssiere B, De Vos S, Auberval M, Vandeghinste N, Dupont S, et al. Analysis of the JAK1 selectivity of GLPG0634 and its main metabolite in different species, healthy volunteers and rheumatoid arthritis patients. *Arthritis Rheum*. 2013;65(10 Suppl):S209–10.
- Namour F, Diderichsen PM, Cox E, Vayssière B, Van der Aa A, Tasset C, et al. Pharmacokinetics and pharmacokinetic/pharmacodynamic modeling of filgotinib (GLPG0634), a selective JAK1 inhibitor, in support of Phase IIB dose selection. *Clin Pharmacokinet*. 2015;54:859–74. <https://doi.org/10.1007/s40262-015-0240-z>.
- Genovese MC, Kalunian K, Gottenberg J-E, Mozaffarian N, Bartok B, Matzkies F, et al. Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomized clinical trial. *JAMA*. 2019;322:315–25. <https://doi.org/10.1001/jama.2019.9055>.
- Combe B, Kivitz A, Tanaka Y, van der Heijde D, Simon JA, Baraf HSB, et al. Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. *Ann Rheum Dis*. 2021;80:848–58. <https://doi.org/10.1136/annrheumdis-2020-219214>.
- Westhovens R, Rigby WFC, van der Heijde D, Ching DWT, Stohl W, Kay J, et al. Filgotinib in combination with methotrexate or as monotherapy versus methotrexate monotherapy in patients with active rheumatoid arthritis and limited or no prior exposure to methotrexate: the phase 3, randomised controlled FINCH 3 trial. *Ann Rheum Dis*. 2021;80:727–38. <https://doi.org/10.1136/annrheumdis-2020-219213>.
- Feagan BG, Danese S, Loftus EV Jr, Vermeire S, Schreiber S, Ritter T, et al. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. *Lancet*. 2021;397:2372–84. [https://doi.org/10.1016/S0140-6736\(21\)00666-8](https://doi.org/10.1016/S0140-6736(21)00666-8).
- European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Assessment report: Jyseleca. EMA/424374/2020. Available from: [https://www.ema.europa.eu/en/documents/assessment-report/jyseleca-epar-public-assessment-report\\_en.pdf](https://www.ema.europa.eu/en/documents/assessment-report/jyseleca-epar-public-assessment-report_en.pdf). Accessed 4 Feb 2021.
- Menet CJ, Fletcher SR, Van Lommen G, Geney R, Blanc J, Smits K, et al. Triazolopyridines as selective JAK1 inhibitors: from hit identification to GLPG0634. *J Med Chem*. 2014;57:9323–42. <https://doi.org/10.1021/jm501262q>.
- Anderson K, Xin Y, Zheng H, Yun C, Kwan E, Qin A, et al. Filgotinib, a JAK1 inhibitor, has no effect on QT interval in healthy subjects. *Clin Pharmacol Drug Dev*. 2020;9:32–40. <https://doi.org/10.1002/cpdd.755>.
- Anderson K, Zheng H, Kotecha M, Cuvin J, Scott B, Sharma S, et al. The relative bioavailability and effects of food and acid-reducing agents on filgotinib tablets in healthy subjects. *Clin Pharmacol Drug Dev*. 2019;8:585–94. <https://doi.org/10.1002/cpdd.659>.
- Van Rompaey L, Galien R, van der Aar EM, Clement-Lacroix P, Nelles L, Smets B, et al. Preclinical characterization of GLPG0634, a selective inhibitor of JAK1, for the treatment of inflammatory diseases. *J Immunol*. 2013;191:3568–77. <https://doi.org/10.4049/jimmunol.1201348>.
- Anderson K, Zheng H, Medzihradsky O, Yizhao L, Qin A, Kearney B, et al. Pharmacokinetics and short-term safety of filgotinib, a selective Janus kinase 1 inhibitor, in subjects with moderate hepatic impairment. *Ann Rheum Dis*. 2019;78(Suppl 2):331.
- Namour F, Desrivot J, Van der Aa A, Harrison P, Tasset C, van't Klooster G. Clinical confirmation that the selective JAK1 inhibitor filgotinib (GLPG0634) has a low liability for drug-drug interactions. *Drug Metab Lett*. 2016;10:38–48. <https://doi.org/10.2174/1872312810666151223103353>.
- Di L. The impact of carboxylesterases in drug metabolism and pharmacokinetics. *Curr Drug Metab*. 2019;20:91–102. <https://doi.org/10.2174/1389200219666180821094502>.
- Namour F, Fagard L, Van der Aa A, Harrison P, Xin Y, Tasset C. Influence of age and renal impairment on the steady state pharmacokinetics of filgotinib, a selective JAK1 inhibitor. *Br J Clin Pharmacol*. 2018;84:2779–89. <https://doi.org/10.1111/bcp.13726>.
- Kavanaugh A, Westhovens RR, Winthrop KL, Lee SJ, Tan Y, An D, et al. Safety and efficacy of filgotinib: up to 4-year results from an open-label extension study of phase II rheumatoid arthritis programs. *J Rheumatol*. 2021;48:1230–8. <https://doi.org/10.3899/jrheum.201183>.
- Tanaka Y, Kavanaugh A, Wicklund J, McInnes IB. Filgotinib, a novel JAK1-preferential inhibitor for the treatment of rheumatoid arthritis: an overview from clinical trials. *Mod Rheumatol*. 2022;32:1–11. <https://doi.org/10.1080/14397595.2021.1902617>.
- Namour F, Vayssiere B, Galien R, Fagard L, Van der Aa A, Harrison P, et al. Filgotinib (GLPG0634), a selective JAK1 inhibitor,

- shows similar PK and PD profiles in Japanese and Caucasian healthy volunteers. *Ann Rheum Dis.* 2015;74(Suppl 2):1063–4.
30. Imai T, Taketani M, Shii M, Hosokawa M, Chiba K. Substrate specificity of carboxylesterase isozymes and their contribution to hydrolase activity in human liver and small intestine. *Drug Metab Dispos.* 2006;34:1734–41. <https://doi.org/10.1124/dmd.106.009381>.
  31. Hsueh C-H, Anderson K, Shen G, Yun C, Qin A, Othman AA. Evaluation of the potential drug interactions mediated through P-gp, OCT2 and MATE1/2K with filgotinib in healthy subjects. *Clin Trans Sci.* 2022;15:361–70. <https://doi.org/10.1111/cts.13152>.
  32. Anderson K, Nelson CH, Gong Q, Alani M, Tarnowski T, Othman AA. Assessment of the effect of filgotinib on the pharmacokinetics of atorvastatin, pravastatin, and rosuvastatin in healthy adult participants. *Clin Pharmacol Drug Dev.* 2022;11:235–45. <https://doi.org/10.1002/cpdd.1015>.
  33. Barbosa ACS, Feng Y, Yu C, Huang M, Xie W. Estrogen sulfotransferase in the metabolism of estrogenic drugs and in the pathogenesis of diseases. *Expert Opin Drug Metab Toxicol.* 2019;15:329–39. <https://doi.org/10.1080/17425255.2019.1588884>.
  34. Tong MH, Jiang H, Liu P, Lawson JA, Brass LF, Song WC. Spontaneous fetal loss caused by placental thrombosis in estrogen sulfotransferase-deficient mice. *Nat Med.* 2005;11:153–9. <https://doi.org/10.1038/nm1184>.
  35. Begley R, Anderson K, Watkins TR, Weng W, Ampaw L, Qin A, et al. Lack of drug-drug interaction between filgotinib, a selective JAK1 inhibitor, and oral hormonal contraceptives levonorgestrel/ethinyl estradiol in healthy volunteers. *Clin Pharmacol Drug Dev.* 2020;10:376–83. <https://doi.org/10.1002/cpdd.870>.
  36. Kavanaugh A, Kremer J, Ponce L, Cseuz R, Reshetko OV, Stanislavchuk M, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). *Ann Rheum Dis.* 2017;76:1009–19. <https://doi.org/10.1136/annrheumdis-2016-210105>.
  37. Westhovens R, Taylor PC, Alten R, Pavlova D, Enríquez-Sosa F, Mazur M, et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). *Ann Rheum Dis.* 2017;76:998–1008. <https://doi.org/10.1136/annrheumdis-2016-210104>.