

ORIGINAL ARTICLE

Influence of age and renal impairment on the steady state pharmacokinetics of filgotinib, a selective JAK1 inhibitor

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Keywords Pharmacokinetics, inflammation < Immunology, elderly < Geriatrics

AIMS

Filgotinib (GS-6034, formerly GLPG0634) is an oral, selective Janus kinase 1 (JAK1) inhibitor that showed early response and sustained efficacy in patients with rheumatoid arthritis and with Crohn's disease. The aim of the present study was to investigate the impact of age and renal impairment (RI) on the pharmacokinetics (PK) of filgotinib and its main metabolite.

METHODS

The effect of age was assessed in two groups of 10 elderly healthy subjects (65–74 and ≥ 75 years of age) and a control group of 10 younger healthy subjects (40–50 years of age). The impact of RI was investigated in three groups of subjects with mild ($n = 6$), moderate ($n = 6$) and severe ($n = 3$) RI [estimated glomerular filtration rate (eGFR) 60–89, 30–59 and 15–29 ml min⁻¹ 1.73 m⁻², respectively] and a control group ($n = 9$) with normal renal function (eGFR ≥ 90 ml min⁻¹ 1.73 m⁻²). The PK of filgotinib and its metabolite were evaluated following filgotinib 100 mg once-daily doses for 10 days.

RESULTS

At steady state, the exposure [area under the concentration–time curve over the dosing interval (AUC_{0–24 h})] of filgotinib and its metabolite was moderately higher (1.45- and 1.33-fold, respectively) in the elderly subjects (≥ 75 years) compared with younger subjects. Renal clearance for filgotinib and its metabolite decreased with the degree of RI, leading to a maximum increase in AUC_{0–24 h} of 1.54-fold for filgotinib and 2.74-fold for the metabolite in subjects with severe RI. Filgotinib was generally safe and well tolerated.

CONCLUSIONS

Age and mild to moderate impairment of renal function had limited impact on the PK of filgotinib. In subjects with severe RI, the exposure to the metabolite of filgotinib was elevated, consistent with its renal elimination pathway.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Filgotinib is an oral, small-molecule, selective Janus kinase 1 inhibitor that combines early response and sustained efficacy in patients with rheumatoid arthritis and Crohn's disease.
- Filgotinib pharmacokinetics (PK) have previously been characterized in healthy subjects and in patients, demonstrating extensive and rapid absorption and dose-proportional PK over a 50–200 mg once-daily dose range.

WHAT THIS STUDY ADDS

- The study found supporting data to indicate that age and mild to moderate impairment of renal function had a limited impact on the PK of filgotinib and its major metabolite.

Introduction

Filgotinib is an oral, small-molecule, selective Janus kinase 1 (JAK1) inhibitor combining early response and sustained clinical efficacy in rheumatoid arthritis (RA) [1–4] and Crohn's disease (CD) [5, 6]. Selectively inhibiting JAK1 may modulate a subset of proinflammatory cytokines within the JAK–signal transducer and activator of transcription (STAT) pathway, which may improve the benefit–risk profile compared with other pan-JAK inhibitors [7].

Filgotinib is a selective JAK1 inhibitor with a half maximal inhibitory concentration (IC_{50}) value of 629 nM (267 ng ml⁻¹); in human whole blood, the compound was 30 times more selective for JAK1 over JAK2 [8, 9]. Filgotinib has a major metabolite with a similar JAK1 selectivity profile but with reduced potency (19-fold) in a human whole-blood assay [8]. In humans, exposure to this metabolite is higher by approximately 16- to 20-fold compared with the parent filgotinib [10]. Filgotinib is extensively and rapidly absorbed after oral dosing, and is metabolized by carboxylesterase isoform 2 (CES2), forming its main metabolite [11]. Systemic exposures of filgotinib and its main metabolite increased dose proportionally over a 50–200 mg once-daily dose (QD) range. Filgotinib and its metabolites are predominantly eliminated in urine (>80%).

RA is a chronic, progressive, systemic inflammatory disease. Lifelong disease-modifying therapy may be required in RA, extending treatment into older patient groups. Hence, characterization of the potential effect of age on filgotinib pharmacokinetics (PK) is important to inform whether dose adjustments may be necessary in the elderly. Various physiological changes that can have an impact on drug disposition are associated with ageing [12], such as reduced muscle mass and total body water, and increased body fat [13]. In addition, a reduction in the apparent liver blood flow with age by about 40% is also expected to affect phase I metabolism rather than phase II conjugation. Although the metabolism of filgotinib is not mediated by cytochrome P450 (CYP450) at the hepatic level, but rather by CES2 at the intestinal level, there is limited information available on the potential impact of ageing on these enzymes. Finally, the most significant organ changes in the elderly occur in the kidneys, with a decline in estimated glomerular filtration rate (eGFR) from 0.40 ml min⁻¹ 1.73 m⁻² to 1.02 ml min⁻¹ 1.73 m⁻² per year.

The current study sought to characterize the effect of ageing and renal impairment (RI) on the PK of filgotinib and its major metabolite, to gain information on optimal dosing and to maximize its benefit : risk profile. Although

the PK of filgotinib are linear (i.e. dose proportional and time independent) within the therapeutic dose range (50–200 mg), the investigations were performed after repeated dosing (100 mg QD), to assess any potential change induced by age and/or decrease in kidney function on the steady-state PK of filgotinib and its main metabolite.

Methods

Two studies were conducted in accordance with the accepted standards for the protection of patient safety and welfare, and the principles of the Declaration of Helsinki and its amendments, and followed Good Clinical Practice. Protocols and informed consent forms for the ageing study and the RI study were approved by the Ziekenhuis Netwerk Antwerpen Ethics Committee (Belgium) and by Ärztekammer Schleswig-Holstein Independent Ethics Committee (Germany), respectively. All subjects gave written informed consent prior to study initiation.

Trial designs

Effect of age (NCT2012-002721-30). The effect of age was evaluated in an open-label phase I study conducted in two groups of 10 healthy elderly subjects (65–74 and ≥ 75 years of age) and one control group of 10 younger subjects (40–50 years of age). Eligible subjects were in good health, with a body mass index (BMI) of 18–30 kg m⁻² and no clinically significant deviation from normal, in terms of medical history, physical examinations, vital signs, electrocardiograms (ECGs) and clinical laboratory determinations. Subjects were excluded from the study if they had history of or a current immunosuppressive condition or the presence or sequelae of gastrointestinal, liver or kidney, or other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs. Subjects had to discontinue all medications (including over-the-counter medications and herbal supplements) within the 2 weeks prior to first dosing. The two groups of elderly subjects have been arbitrarily defined to cover subjects aged from 65 years and also in the older age range, 75 years and above. All subjects (male and female) were matched for body weight across each age group.

After a standard breakfast, filgotinib 100 mg (capsule formulation) was administered QD for 10 days. Blood samples were collected for filgotinib and its metabolite on day 10 at the following times: predose and at 0.5, 1, 2, 3, 5, 8, 12, 24, 48 and 72 h postdose. Additional predose samples

were collected on days 1, 2, 3, 5 and 7 for steady-state assessment. Urine was collected in three fractions on day 10 (0–6, 6–12, 12–24 h after dosing). Additionally, urine samples were collected on day 1 over 24 h to calculate the creatinine clearance (CL_{CR}) and estimate the potential decline in renal function in elderly subjects.

Effect of RI (NCT2013-004407-40). The effect of RI was evaluated in an open-label phase I study conducted in healthy male and female subjects between 18–79 years of age, with a BMI of 18–34 kg m⁻² and with various degrees of RI, categorized according to the eGFR using the modification of diet in renal disease equation. As filgotinib is predominantly eliminated via metabolism, the effect of RI was firstly assessed in three subjects with an eGFR between 15 and 29 (inclusive) ml min⁻¹ 1.73 m⁻² as a ‘worst case’ scenario to determine the magnitude of the change in PK in these subjects with severe RI. The PK and safety data from these three subjects were compared with those of three subjects with normal renal function. Given the substantial changes noted for the metabolite (more than twofold increase in exposure) [14], the study was expanded to investigate further the changes in PK in subjects with moderate (eGFR: 30–59 ml min⁻¹ 1.73 m⁻²) and mild (eGFR: 60–89 ml min⁻¹ 1.73 m⁻²) RI in comparison with PK from subjects with normal renal function. For this second step, six subjects were enrolled for each renal function group. For the final PK analysis, data from subjects with normal renal function included in the two study steps were pooled ($n = 9$).

Subjects with normal renal function were matched to the RI subjects, in terms of median age (± 10 years) and BMI ($\pm 15\%$). Eligible subjects were in good health and in stable condition with regard to renal function, based on the results of medical history, physical examinations, vital signs, 12-lead ECG and clinical laboratory determinations. Subjects were excluded from the study if they had a history of or a current immunosuppressive condition or a history of gastric surgery, vagotomy and bowel resection, or any surgical procedures known to interfere with the gastrointestinal motility, pH or absorption. Additionally, to control for potential influences derived from the natural course of the renal dysfunction and demonstrate the stability of the RI, the variation in serum creatinine level was measured 3–6 months prior to screening and at the time of screening; this variation should be $< 20\%$. Subjects with normal renal function had to discontinue all concomitant medications (including over-the-counter medications and herbal supplements) within the 2 weeks prior to first dosing. The same restrictions applied for RI subjects, with the exception of medications essential for the treatment of concomitant medical conditions and the management of RI.

After a 10-h fast, filgotinib 100 mg (tablet formulation) was administered QD for 10 days. Food had no impact on the bioavailability of filgotinib [10]; however, to prevent any issues at dosing intake in these subjects, the tablet was given in a fasted state. Blood samples were collected to evaluate the PK of filgotinib and its metabolite on day 10 at the following times: predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 8, 12, 24, 48, 72 and 168 h after dosing. Trough plasma concentrations were determined at days 1, 2, 3, 5, 7 and 8 for steady-state assessment. Urine was collected in three fractions on day 10 (0–6, 6–12 and 12–24 h after dosing).

Blood and urine sample management

Blood was collected in tubes containing lithium heparin to obtain plasma for the analysis of concentrations of filgotinib and its major metabolite. Within 30 min after blood collection, the plasma was separated in a refrigerated centrifuge (4–8°C) for 10 min at approximately 1500 g and stored at –20°C until analysis. Urine samples were collected and refrigerated (2–8°C) until sample collection was completed. After measuring the total weight, the urine was homogenized and 10 ml aliquots were placed into prelabelled polypropylene containers and stored at –20°C until analysis.

Bioanalytical and PK assessments

Plasma and urine concentrations of filgotinib and its major metabolite were determined using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) assay [10]. The internal standard (deuterated filgotinib) was added to plasma samples and then processed by solid phase extraction. The evaporated and reconstituted samples were injected into a SCIEX API3000 LC–MS/MS equipped with a short high-pressure LC column. Filgotinib and its metabolite were detected with multiple reaction monitoring. Quantification was performed using peak area ratios and standard curves (with $1/x^2$ least squares quadratic regression) prepared from calibration standards. The lower limit of quantification for filgotinib and its metabolite was 1.00 ng ml⁻¹. For both compounds, the between- and within-run precision for quality controls was expressed as the coefficient of variation (CV%) and was no greater than 8.7% and 8.5%, respectively, with deviations from nominal concentrations of no more than 12.0%.

For urine samples, the between- and within-run precision for quality controls for filgotinib and its metabolite was expressed as CV% and was no greater than 11.0% and 12.9%, respectively, with deviations from nominal concentrations of no more than 14.0%.

The steady-state PK parameters for filgotinib and its metabolite included: maximum plasma concentration (C_{max}), the time of occurrence of C_{max} (t_{max}), the apparent terminal half-life ($t_{1/2,zz}$), the area under the curve over the dosing interval ($AUC_{0-24 h}$), the metabolite-to-parent ratio (R) evaluated using $AUC_{0-24 h}$, the amount excreted in the urine (A_e) and the renal clearance (CL_R) calculated over the dosing interval. These PK parameters were determined using WinNonLin® (version 5.3), Pharsight Corporation, Mountain View, CA, USA.

Safety assessments

General safety was evaluated by the incidence of adverse events through nonleading questioning, vital signs, 12-lead ECGs, physical examinations and clinical laboratory parameters (haematology, biochemistry and urinalysis).

Statistical analyses

No formal sample size calculations were performed for either study. The number of subjects per group was considered sufficient to allow for relevant comparisons of PK and safety data among subjects with various degrees of RI or of different ages. Descriptive statistics for the PK parameters were calculated. For each group of elderly or RI subjects, the fold-change in exposure (C_{max} and $AUC_{0-24 h}$) vs. control subjects (i.e. young

or normal renal function groups) was calculated as the point estimate with its associated 90% confidence interval (CI) of the least-square geometric means of the mixed-effect analysis of variance, with age group or stage of RI as fixed factor, and represented graphically. Additionally, the relationship between PK parameters and renal function (CL_{CR} or eGFR) was explored in both studies.

The impact of age and RI on the PK of filgotinib and its metabolite was assessed, taking into account both the magnitude of the change and the statistical analysis. A fold-change in mean PK parameters for filgotinib or its metabolite ≤ 2 was considered as moderate and of no clinical relevance. In addition, for all 90% CIs that contained the value of one, the observed fold-change was considered as not statistically significant.

Results

Subject disposition and baseline characteristics

Subject disposition is presented in Table 1. Most of the subjects included in the two studies (96.7% and 100%, respectively) were Caucasian. In the study to assess the effect of age, males were predominant in the two elderly groups (70–80%), and females (80%) in the younger control group. In the RI study, most of subjects were male in each subgroup (66.7–100%). The other demographic and baseline characteristics across subgroups, except for age and renal function, were comparable.

Effect of age

A summary of PK parameters for filgotinib and its metabolite at day 10 of dosing is shown in Table 2. After repeated daily oral administration, filgotinib was rapidly absorbed, followed by a biphasic decline in plasma concentrations (Figure 1). Sequential predose (trough) concentrations are shown in Figure 2, demonstrating no accumulation with repeated dosing. Filgotinib plasma concentrations reached steady state by the second dosing day, regardless of the age group.

A graphical representation of the fold-change (with 90% CI) in C_{max} and $AUC_{0-24\ h}$ of filgotinib between elderly age groups relative to the younger control group is presented in Figure 3. Overall, there were no or minimal differences between age groups for all PK parameters, as shown by the 90% CI containing the value of one, except for exposure ($AUC_{0-24\ h}$), with a maximal increase of 1.40-fold observed in the oldest vs. youngest age group. The percentage of filgotinib excreted in the urine was not affected by age, with mean values of 6.55% and 7.24% of the daily dose administered for the two elderly age groups, respectively, compared with 8.01% for the younger control group. As a consequence, CL_R was 34% lower in the oldest compared with the youngest age group.

Of note, even though CL_{CR} in the oldest age group was slightly (~20%) lower than in the two other age groups (Table 1), the values were still within the normal range, indicating no RI in these subjects. The decrease in filgotinib CL_R was poorly associated with a decrease in CL_{CR} (Figure 4).

The main metabolite was formed rapidly, with a median t_{max} ranging between 3.0 h and 5.0 h, and was slowly

Table 1

Demographic summary

Group	N	Age (years)	Height (cm)	Weight (kg)	BMI ($kg\ m^{-2}$)	Sex (F:M)	Race (Caucasian: Black)	Renal function
Ageing study (N = 36)								
Age 40–50	10	46.0 (41–50)	167 (154–181)	Median values (range) 72.5 (68–83)	25.4 (23.2–29.5)	8:2	10:0	CL_{CR} 127 (95.0–158)
Age 65–74	10	67.5 (65–72)	172 (157–182)	74.5 (69–81)	25.7 (23.2–30.0)	2:8	9:1	115 (77.4–135)
Age ≥ 75	10	78.0 (75–81)	167 (153–173)	72.5 (62–90)	26.9 (22.6–30.1)	3:7	10:0	103 (81.9–136)
RI study (N = 24)								
Normal renal function								
	9	65.0 (63–78)	175 (160–185)	Median values (range) 77.6 (66.4–101)	26.0 (24.0–30.0)	2:7	6:0	eGFR ^a ($ml\ min^{-1}\ 1.73\ m^{-2}$) 101.0 (94.0–116.0)
Mild RI	6	71.0 (60–79)	171 (158–182)	70.0 (54.0–102)	24.5 (19.0–34.0)	3:3	6:0	73.5 (61.0–75.3)
Moderate RI	6	69.0 (47–78)	173 (163–174)	76.2 (58.2–81.0)	25.5 (20.0–30.0)	2:4	6:0	47.5 (33.0–54.0)
Severe RI	3	73.0 (71–77)	170 (170–180)	85.8 (75.0–108)	30.0 (26.0–33.0)	0:3	3:0	22.0 (15.0–25.0)

BMI, body mass index; CL_{CR} , creatinine clearance after the dose (day 1); eGFR, estimated glomerular filtration rate; F, female; M, male; RI, renal impairment

^aAccording to Modification in Diet in Renal Disease equation

Table 2

Summary of filgotinib and metabolite steady-state pharmacokinetic parameters and corresponding creatinine clearance across age groups

	PK parameter	Age 40–50 years; N = 10	Age 65–74 years; N = 10	Age ≥75 years; N = 10
Filgotinib	C_{\max} ($\mu\text{g mL}^{-1}$)	0.435 (32.4)	0.584 (39.3)	0.629 (32.1)
	t_{\max} (h)	2.0 (1.0–5.0)	2.0 (0.5–3.0)	2.0 (0.5–3.0)
	$\text{AUC}_{0-24\text{ h}}$ ($\mu\text{g}\cdot\text{h mL}^{-1}$)	1.60 (32.0)	1.79 (24.0)	2.22 (20.6)
	$t_{1/2, \lambda z}$ (h)	6.07 (58.2) ^a	5.83 (23.3) ^b	6.90 (36.3) ^a
	$\text{Ae}_{0-24\text{ h}}$ (% dose)	8.01 (26.5) ^b	6.55 (14.3) ^c	7.24 (16.9) ^b
	CL_R (L h^{-1})	5.55 (19.9) ^b	3.90 (23.2) ^c	3.33 (20.2) ^b
Metabolite	C_{\max} ($\mu\text{g mL}^{-1}$)	1.69 (26.5)	1.90 (15.5)	2.20 (19.4)
	t_{\max} (h)	4.0 (2.0–5.0)	3.0 (3.0–5.0)	5.0 (3.0–5.0)
	$\text{AUC}_{0-24\text{ h}}$ ($\mu\text{g}\cdot\text{h mL}^{-1}$)	29.4 (27.3)	34.2 (17.3)	40.9 (21.9)
	$t_{1/2, \lambda z}$ (h)	17.8 (17.9)	24.7 (23.3)	23.5 (21.2)
	$\text{Ae}_{0-24\text{ h}}$ (% dose)	34.3 (22.3) ^b	37.4 (13.2) ^c	37.6 (15.4) ^b
	CL_R (L h^{-1})	1.25 (19.3) ^b	1.13 (20.9) ^c	0.926 (29.5) ^b
	R	18.8 (25.1)	19.4 (22.0)	18.4 (16.4)
Creatinine clearance	CL_{cr} (mL min^{-1})	127 (12.8)	111 (16.3)	100 (15.5)

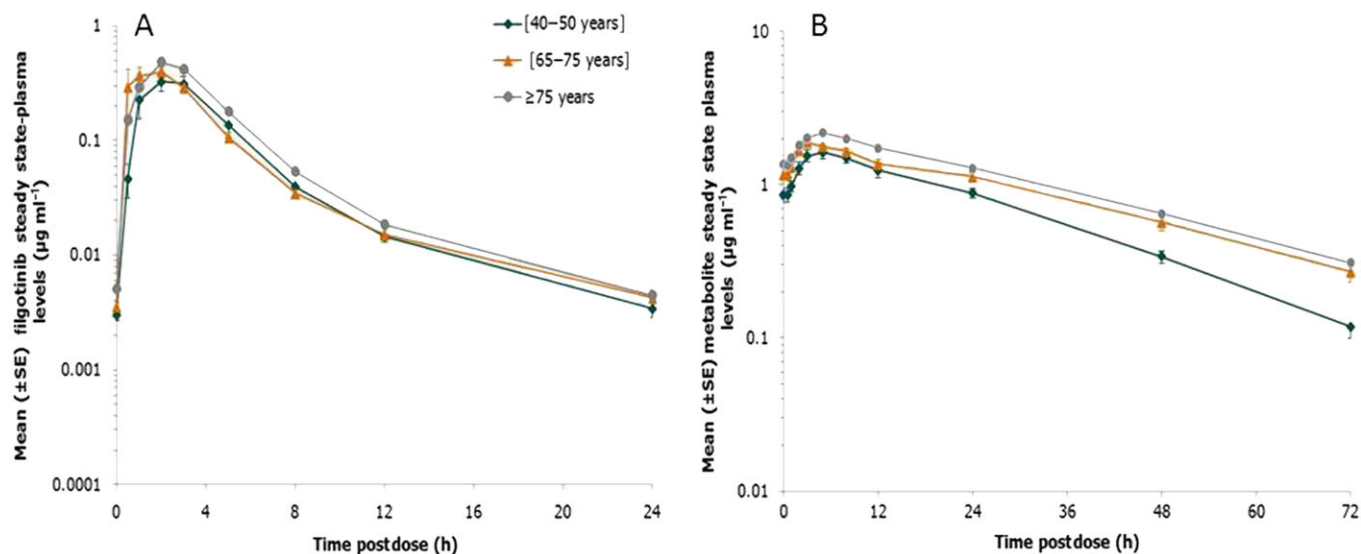
Values are arithmetic means (CV%) except median (min–max) for t_{\max} and geometric means (CV%) for R

$\text{Ae}_{0-24\text{ h}}$, amount of filgotinib or metabolite excreted in the urine over 24 h, expressed as a percentage of daily dose administered; $\text{AUC}_{0-24\text{ h}}$, area under the curve over the dosing interval; CL_R , renal clearance; C_{\max} , maximum plasma concentration; PK, pharmacokinetic; R, metabolite-to-parent ratio; t_{\max} , time of occurrence of C_{\max} ; $t_{1/2, \lambda z}$, apparent terminal half-life

^aN = 7

^bN = 8

^cN = 9

**Figure 1**

Mean [\pm standard error (SE)] steady-state plasma concentration vs. time profiles of filgotinib (A) and its metabolite (B) in the three age groups following dosing with filgotinib 100 mg once daily. Note: There is a 10-fold difference in the y-axis scale

eliminated according to a mono-exponential decline (Figure 1). Steady state was attained within 4 dosing days (Figure 2), consistent with the $t_{1/2, \lambda z}$ of approximately 22 h.

An overall increase of 1.25-fold in C_{\max} and of 1.33-fold in $\text{AUC}_{0-24\text{ h}}$ was noted in the oldest vs. youngest age groups

(Figure 3). Additionally, the percentage of filgotinib metabolite excreted unchanged in the urine was not affected by age: 34.3% and 37.6% of the daily dose administered for the youngest group (40–50 years) and oldest group (≥ 75 years), respectively. Consequently, CL_R was 40% lower in the oldest ($\text{CL}_R =$

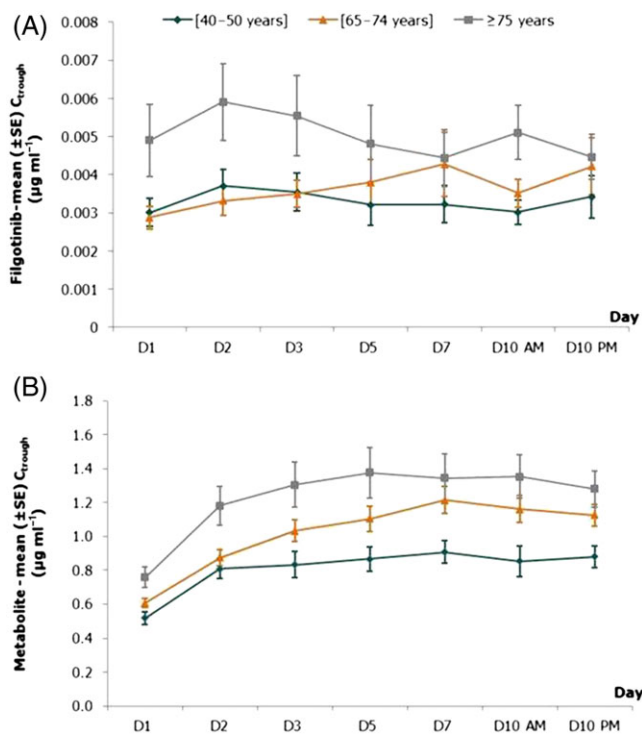


Figure 2

Mean [\pm standard error (SE)] predose (trough) plasma concentrations of filgotinib (A) and its metabolite (B) in the three age groups following dosing with filgotinib 100 mg once daily

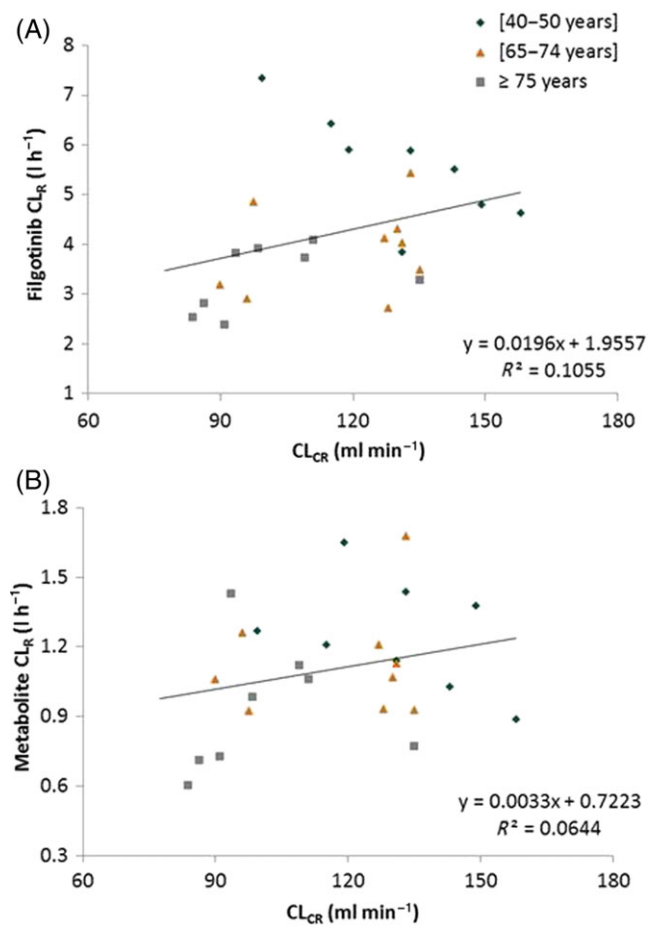


Figure 4

Relationship between the steady-state renal clearance (CL_R) of filgotinib (A) and its metabolite (B), and creatinine clearance (CL_{CR})

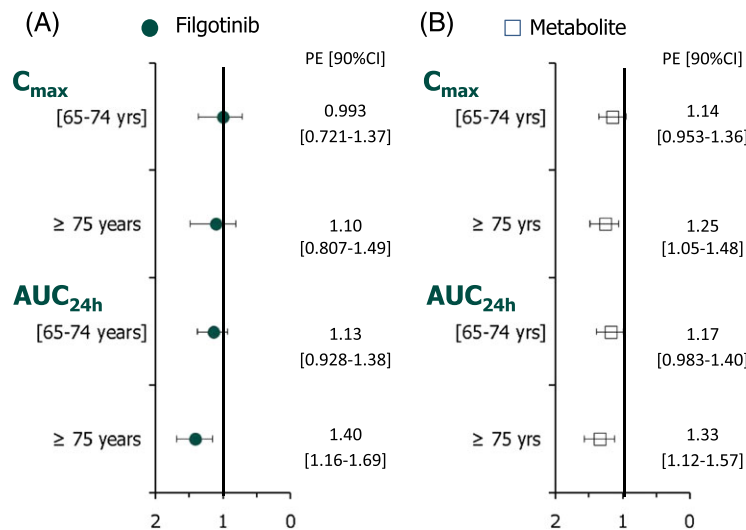


Figure 3

Fold-change (90% CI) in steady-state C_{max} and $AUC_{0-24 h}$ of filgotinib (A) and its metabolite (B) in elderly subjects (65–74 and ≥ 75 years) relative to young subjects (40–50 years). $AUC_{0-24 h}$, area under the curve over the dosing interval; CI, confidence interval; C_{max} , maximum plasma concentration; PE point estimate

0.926 l h⁻¹) compared with the youngest (CL_R = 1.25 l h⁻¹) age group. In regard to filgotinib, the decrease in metabolite CL_R was not associated with a decrease in CL_{CR} (Figure 4).

The apparent elimination half-life (t_{1/2}) of filgotinib (mean range: 5.83–6.90 h) was not altered by age. For the metabolite, the apparent elimination t_{1/2,λz} was similar for the two elderly groups (24.7 h and 23.5 h, respectively) but slightly longer than for the youngest (17.8 h). PK differences between age groups were similar between filgotinib and its metabolite, as reflected by similar R values across the three age groups.

In all age groups, the between-subject variability was low to moderate, as reflected by CV% of C_{max} and AUC_{0–24 h} lower than 40% for both filgotinib and its metabolite.

Effect of RI

A summary of PK parameters for filgotinib and of its major metabolite at day 10 of dosing is shown in Table 3. Filgotinib was rapidly absorbed, with C_{max} reached 1 h after dosing on day 10 (Figure 5). Sequential predose (trough) concentrations are shown in Figure 6, demonstrating that steady state for filgotinib concentrations in the plasma was reached by day 2 in all renal function groups. No accumulation was observed, which was consistent with the short t_{1/2,λz} (5.42–10.9 h) and the QD dosing interval. In all groups, the between-subject variability, as reflected by the CV% of AUC_{0–24 h} and C_{max}, was moderate to high after multiple dosing (CV% up to 60%).

RI reduced the Ae over 24 h (Ae_{0–24 h}), which decreased with the degree of RI. Consequently, the CL_R decreased with the degree of RI, leading to 1.54- and 1.42-fold higher filgotinib plasma exposure (AUC_{0–24 h}) in subjects with severe and moderate RI, respectively, compared with subjects with normal renal function (C_{max} did

not appear to differ according to stage of RI). However, the 90% CI of the fold-change vs. control group included the value of one and suggested that these changes observed in the AUC_{0–24 h} of filgotinib for moderate and severe RI were not significant (Figure 7).

For the metabolite, steady-state plasma concentrations were reached between day 3 (normal renal function and mild RI) and day 5 (moderate and severe RI), consistent with mean t_{1/2,λz} values ranging from 20.8 h (normal renal function) to 43.6 h (severe RI), as shown in Figure 6. A graphical representation of the fold-change differences in C_{max} and AUC_{0–24 h} between RI groups relative to the group with normal renal function is presented in Figure 7. RI showed a marked effect on the metabolite exposure (C_{max}, AUC_{0–24 h}), as well as its elimination parameters (t_{1/2,λz} and CL_R). In the severe RI group, the reduction in its elimination (mean CL_R values 0.488 vs. 1.59 l h⁻¹ and mean t_{1/2} values 43.6 vs. 20.8 h) resulted in 2.17- and 2.74-fold higher C_{max} and AUC_{0–24 h}, respectively, compared with subjects with normal renal function. In the two other RI groups, no or a minimal effect was noted vs. the control group, except for moderate RI, with a 1.67-fold increase in AUC_{0–24 h}. In all groups, the between-subject variability reflected by the CV% of AUC_{0–24 h} and C_{max} was low to moderate after multiple dosing (up to 38.4%).

The relationships between exposure to filgotinib and its metabolite (AUC_{0–24 h} and C_{max}) and eGFR are illustrated in Figure 8. The correlation coefficient was higher for the metabolite than the parent drug, filgotinib.

Safety

There were no deaths or serious adverse events during either study. In the current studies, none of the treatment-emergent adverse events were severe in intensity and none led to

Table 3

Summary of steady state pharmacokinetic parameters for filgotinib and its metabolite across renal impairment groups

	PK parameter	Normal renal function N = 9	Mild RI N = 6	Moderate RI N = 6	Severe RI N = 3
Filgotinib	C _{max} (μg ml ⁻¹)	0.882 (58.2)	0.780 (60.3)	0.936 (47.7)	0.921 (12.1)
	t _{max} (h)	0.8 (0.3–1)	0.5 (0.3–2)	0.6 (0.3–4)	1 (1–1)
	AUC _{0–24 h} (μg.h ml ⁻¹)	1.82 (51.4)	1.89 (29.0)	2.69 (42.5)	2.64 (34.2)
	t _{1/2,λz} (h)	5.42 (30.2)	10.9 (47.1)	10.6 (75.4)	9.03 (51.3)
	Ae _{0–24 h} (% dose)	7.61 (35.4)	5.37 (42.1)	4.34 (51.2)	2.08 (34)
	CL _R (l h ⁻¹)	4.45 (27.4)	2.95 (48.1)	1.89 (61.4)	0.898 (65)
Metabolite	C _{max} (μg ml ⁻¹)	1.63 (31.9)	1.54 (31.3)	2.35 (35.4)	3.43 (14.6)
	t _{max} (h)	3 (2–4)	3.3 (1.5–5)	2.3 (0.5–5)	3 (3–4)
	AUC _{0–24 h} (μg.h ml ⁻¹)	24.9 (31.7)	30.1 (29.3)	42.7 (38.4)	66.6 (18.5)
	t _{1/2,λz} (h)	20.8 (17.1)	25.4 (24.8)	31.7 (24.9)	43.6 (12.6)
	Ae _{0–24 h} (% dose)	37.4 (11.6)	35.7 (40.3)	29.9 (24.1)	32.1 (9.36)
	CL _R (l h ⁻¹)	1.59 (24.5)	1.21 (42.1)	0.781 (47.8)	0.488 (10.6)
Renal function	R	13.8 (21.5)	15.9 (22.0)	16.7 (35.8)	26.0 (20.4)
	eGFR (ml min ⁻¹ /1.73 m ⁻²)	102.1 (2.58)	71.9 (2.21)	45.0 (3.69)	20.7 (2.96)

Values are arithmetic means (CV%) except median (min–max) for t_{max}, geometric means (CV%) for R and arithmetic mean (standard error) for estimated eGFR. Ae_{0–24 h}, amount of filgotinib or metabolite excreted in the urine over 24 h, expressed as a percentage of daily dose administered; AUC_{0–24 h}, area under the curve over the dosing interval; CL_R, renal clearance; C_{max}, maximum plasma concentration; eGFR, estimated glomerular filtration rate according to Modification in Diet in Renal Disease equation; PK, pharmacokinetic; R, metabolite-to-parent ratio; t_{max}, time of occurrence of C_{max}; t_{1/2,λz}, apparent terminal half-life

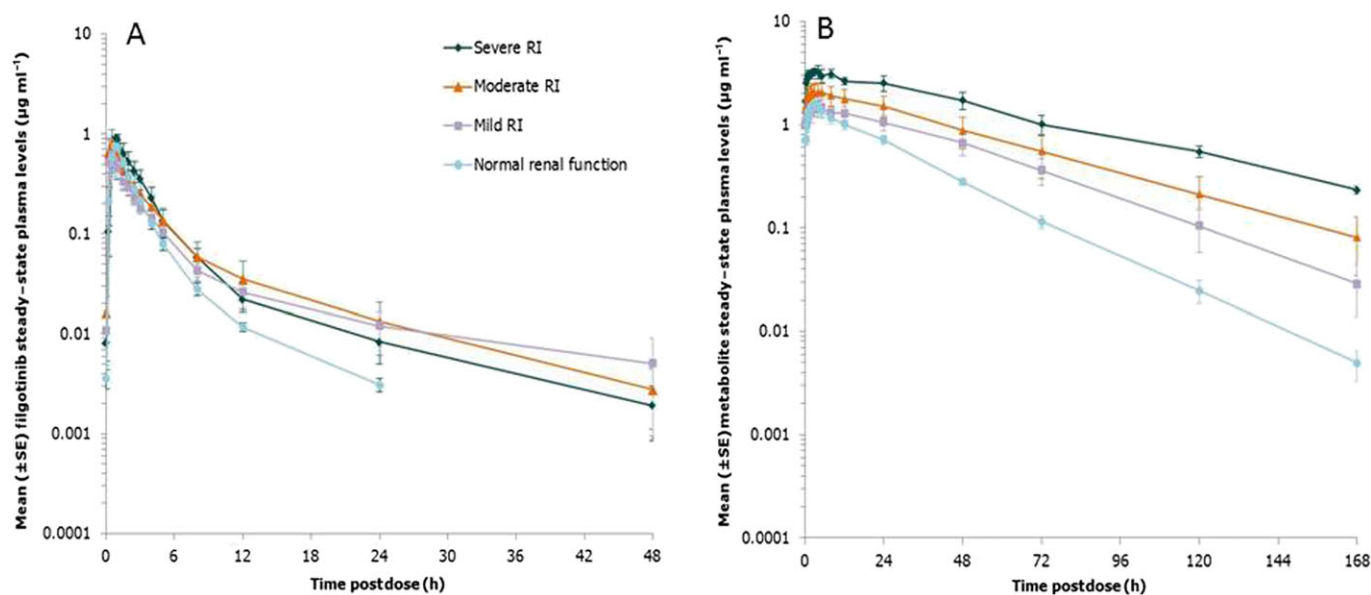


Figure 5

Mean \pm standard error (SE)] steady-state plasma concentration vs. time profiles of filgotinib (A) and its metabolite (B) in subjects with various degrees of renal impairment following dosing with filgotinib 100 mg once daily. RI, renal impairment

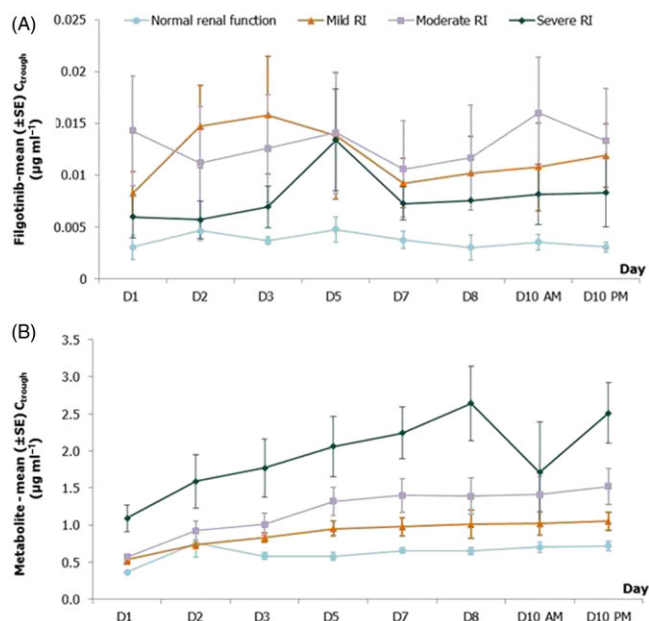


Figure 6

Mean \pm standard error (SE)] predose (trough) plasma concentrations of filgotinib (A) and its metabolite (B) in subjects with various degrees of renal impairment following dosing with filgotinib 100 mg once daily. RI, renal impairment

study medication withdrawal, although three of them were of moderate severity: migraine (age study), urinary continence (age study) and headache (RI study). There were no clinically significant changes in laboratory values, physical examination, vital signs, or ECG parameters. Filgotinib 100 mg QD for 10 days was generally safe and well tolerated in these studies.

Discussion

Two phase I open-label studies were conducted to examine the effects of age and RI on the steady-state PK of filgotinib and its major metabolite. Although most of the subjects included in these two studies were Caucasian (>96%) and males were predominant in the two elderly groups (70–80%) and in

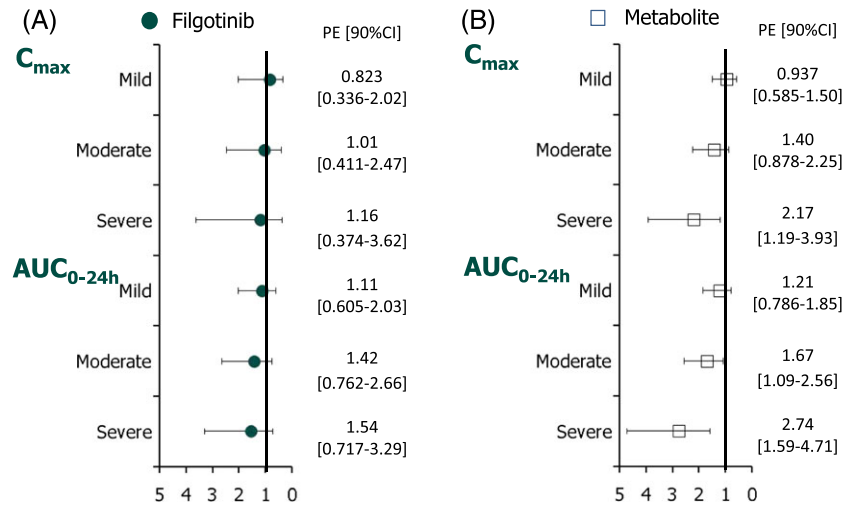


Figure 7

Fold-change (90% CI) in steady-state C_{max} and $AUC_{0-24 h}$ of filgotinib (A) and its metabolite (B) in subjects with mild, moderate and severe renal impairment relative to subjects with normal renal function. $AUC_{0-24 h}$, area under the curve over the dosing interval; CI, confidence interval; C_{max} , maximum plasma concentration; PE point estimate

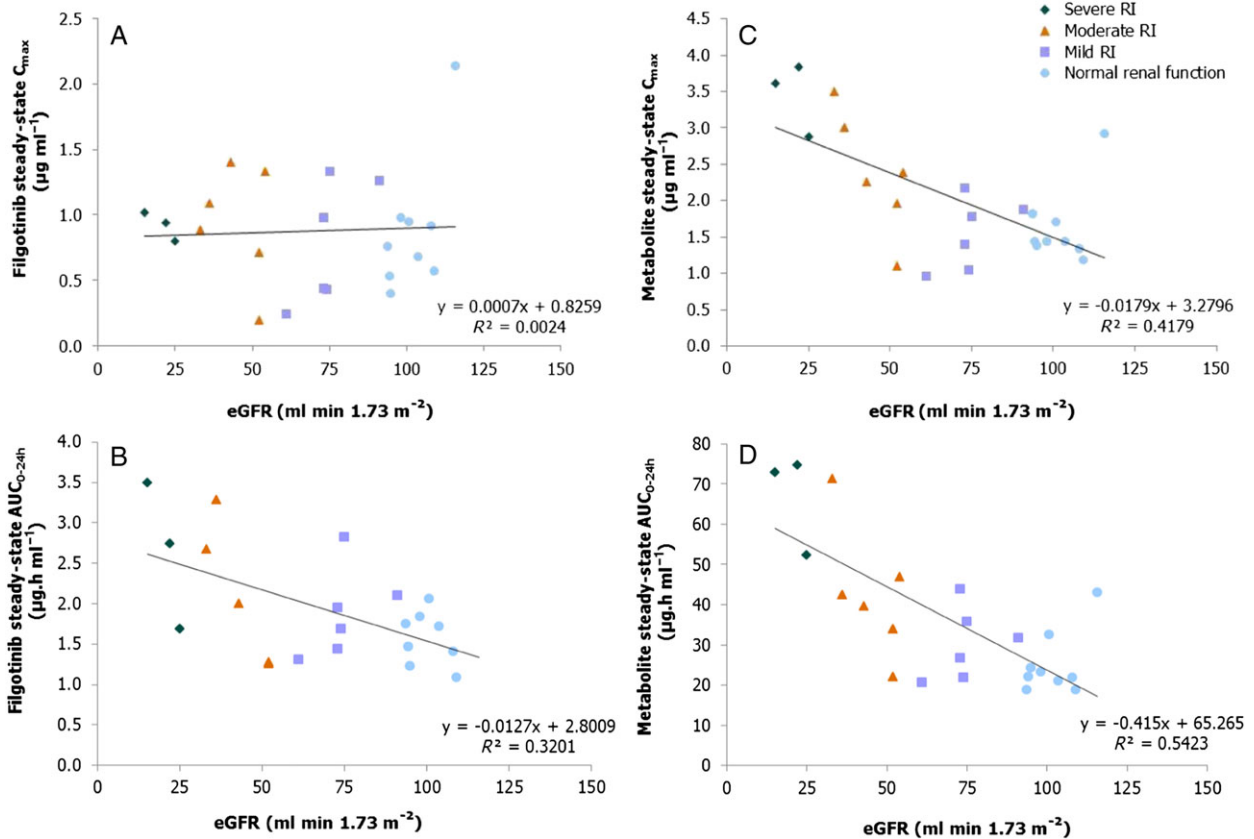


Figure 8

Relationship between steady-state exposure (C_{max} and AUC_{tau}) of filgotinib (A and B) and its metabolite (C and D) and eGFR. $AUC_{0-24 h}$ = area under the curve over the dosing interval, C_{max} , maximum plasma concentration; eGFR, estimated glomerular filtration rate; RI, renal impairment

each RI group (66.7–100%), this was not expected to confound the potential effect of age or renal function on filgotinib PK, as none of the demographic factors (e.g. sex, body weight, BMI, race) were shown significantly to affect filgotinib PK, based on population PK analysis using phase II data in RA and CD [15–17].

Although these two studies used different filgotinib formulations and administration conditions (the effect of age study used a capsule formulation in fed conditions and the RI study used a tablet formulation in the fasted state), filgotinib and metabolite exposure appeared to be comparable for the control groups across these two studies.

No change in PK was noted in the 65–74-year age group. Filgotinib exposure ($AUC_{0-24\text{ h}}$) was moderately higher, by 1.40-fold, in subjects aged ≥ 75 years, while C_{max} , $t_{1/2,\lambda z}$ and A_e for unchanged filgotinib were not altered. The CL_R decreased with age, as did the CL_{CR} , but without a strong relationship between these parameters. Of note, even though CL_{CR} was lower in elderly subjects, the values were still within the normal range, indicating that there was no RI in these subjects.

Higher gastric pH may have been a factor for differences in bioavailability in elderly subjects [18, 19]; however, for filgotinib administered as the hydrochlorhydrate salt in these two studies, a higher gastric pH would have led to filgotinib free base formation, which is less soluble and bioavailable than the ionized form. Consequently, higher gastric pH would be unlikely to account for the observed increase in exposure in the elderly subjects aged ≥ 75 years.

Similarly to filgotinib, exposure to the metabolite was higher (by 1.33-fold) in the oldest subjects after filgotinib 100 mg QD, with no change in the formation and elimination of the metabolite. This observation was supported by the constant R values over the entire age range (from 18.4 to 19.4). Based on these data, it could be concluded that age had no impact on the carboxylesterases involved in filgotinib's metabolite formation. Overall, the moderate change (<2-fold) observed in exposure of filgotinib and its metabolite are unlikely to be linked to physiological changes associated with age and could be due to variability and the small sample size ($n = 10$ per age group). This is further support by the population PK model developed with data obtained in patients with RA [15] and CD [16, 17], in which age was not included as a significant covariate in the PK modelling of filgotinib and its metabolite.

In the RI study, filgotinib CL_R decreased with the degree of RI, with an 80% lower value for subjects with severe RI (0.898 l h^{-1}), compared with subjects with normal renal function (4.45 l h^{-1}). The decrease in CL_R in severe RI subjects resulted in a moderate increase in filgotinib systemic exposure (by 1.54-fold vs. normal). For the metabolite, C_{max} and $AUC_{0-24\text{ h}}$ increased with the degree of RI severity. At the extremes of renal function (i.e. severe RI compared with normal renal function), the mean values of C_{max} and $AUC_{0-24\text{ h}}$ increased by 2.17-fold and 2.74-fold, respectively. In the two other RI groups, no or a minimal effect was noted vs. the control group, except for moderate RI with a 1.67-fold increase in $AUC_{0-24\text{ h}}$. The $t_{1/2,\lambda z}$ of the filgotinib metabolite was also longer according to RI severity: 20.8 h and 25.4 h for subjects with normal renal function or mild RI, and 31.7 h and 43.6 h for subjects with moderate and severe RI, respectively. The CL_R decreased with the degree of RI, with a

51% and 69% drop in the moderate and severe renal RI groups (0.781 l h^{-1} and 0.488 l h^{-1}), respectively, compared with subjects with normal renal function (1.59 l h^{-1}) or mild RI (1.21 l h^{-1}).

Although the number of subjects included in each RI group was small ($n = 3-6$), the results of the present study showed a clear trend of increased exposure associated with decreased renal function. The observed differences in exposure to the metabolite were more pronounced compared with the parent drug, which was consistent with the fact that, in humans, filgotinib is mainly metabolized, with only a small fraction (<10%) excreted unchanged in the urine, whereas its metabolite is excreted mainly in the urine ($\geq 50\%$). In terms of the impact of age and RI, a two-fold increase in mean exposure was defined as a substantial effect and used as the threshold for interpretation. Based on this criterion, a significant change >2-fold was observed for the metabolite exposure in severe RI only.

Clinical efficacy was observed at daily doses of 75–300 mg in a phase IIa study in patients with RA with an insufficient response to methotrexate and naïve to biological disease-modifying anti-rheumatic drugs, with similar effects noted for these doses in terms of improvements in C-reactive protein and disease activity scores based on 28 joints [1, 2, 20]. Subsequently, efficacy was confirmed in larger, phase IIb studies of filgotinib given as monotherapy [3] and in combination with methotrexate [4]. Filgotinib dosed at 100–200 mg once daily is currently being evaluated in pivotal phase III studies in patients across several indications, including RA, CD and ulcerative colitis.

Conclusions

Age and mild to moderate RI had a limited impact on the PK of filgotinib. In subjects with severe RI, the exposure to filgotinib's metabolite was elevated, consistent with its renal elimination pathway.

Competing Interests

F.N. is an employee of Galapagos SASU. L.F., A.V. der A., P.H. and C.T. are employees of Galapagos NV. Y.X. is an employee of Gilead Sciences.

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