

Pharmacokinetics and Safety of Single and Multiple Doses of Peficitinib (ASP015K) in Healthy Chinese Subjects

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Objective: To investigate the pharmacokinetics and safety of peficitinib (Janus kinase inhibitor for the treatment of rheumatoid arthritis) in healthy Chinese subjects following single and multiple doses.

Methods: This open-label, randomized study was conducted at one site in China. Subjects received peficitinib 50, 100 or 150 mg as a single dose on Day 1 (fasted) and once daily from Days 8 to 13 in the multiple-dose period (fed). Blood samples were collected before administration each day, and up to 72h post administration. Pharmacokinetic assessments included area under the concentration curve (AUC), half-life ($t_{1/2}$), maximum concentration (C_{max}), and time to maximum concentration (t_{max}) of peficitinib and its metabolites (H1, H2 and H4). Treatment-emergent adverse events (TEAEs) were evaluated.

Results: Thirty-six subjects were enrolled (12 per dose group). After a single dose of peficitinib, median t_{max} was 1.0–1.5h and mean $t_{1/2}$ was 7.4–13.0h for all doses. In the multiple-dose period, median t_{max} was 1.5–2.0h. Dose-proportional increases in C_{max} and AUC_{24h} were observed for peficitinib and its metabolites following single and multiple doses, with minimal drug accumulation. The major metabolite was H2, with a systemic exposure of >150% of the parent AUC. Drug-related TEAEs were experienced by 5 (13.9%) and 12 (33.3%) subjects in the single- and multiple-dose periods, respectively. Following multiple doses of peficitinib, TEAEs were more frequent in higher than lower dose groups but were mild in severity with no related discontinuation or death.

Conclusion: Following single and multiple doses of peficitinib in healthy Chinese subjects, peficitinib demonstrated rapid absorption and was well tolerated at all doses.

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Keywords: rheumatoid arthritis, treatment, dose-proportionality, tsDMARDs

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes systemic inflammation of the synovial tissues of various joints.¹ The primary goal of RA therapy is to reduce disease activity and achieve remission by controlling typical complications of RA such as inflammation, loss of function, pain and reduced patient quality of life.^{2–4}

For patients who have had an inadequate response to standard RA therapies, such as methotrexate (MTX), alternative treatment options are increasing.⁵ The 2019 EULAR recommendations revised the preference of biological disease-modifying antirheumatic drugs (bDMARDs) over targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) in the treatment of RA because of new evidence supporting the long-term efficacy and safety of Janus kinase inhibitors (JAKis). As such, there is no preference in the guidelines between bDMARDs and tsDMARDs for early

combination therapy with conventional DMARDs (such as MTX).⁵ However, the continued development of agents with alternative modes of action, such as tsDMARDs (including JAKis), is important to further expand upon the current treatment options available for patients with RA.^{4–9}

Peficitinib is a novel oral tsDMARD that has pan-Janus kinase (JAK) inhibitory activity. It has been shown to be effective as a monotherapy in RA treatment in a randomized phase IIb study at doses of 25, 50, 100, and 150 mg/day,¹⁰ and in combination with other DMARDs or MTX in two randomized phase III studies at doses of 100 and 150 mg/day,^{11,22} with good tolerability over a 2-year treatment period.¹² Peficitinib has been approved for the treatment of patients with RA in Japan (2019) and Taiwan (2020).^{13–15} It has also demonstrated rapid dose-proportional absorption after single- and multiple-dose administration;¹⁶ however, absorption is delayed by a food effect following a moderate- to high-fat meal.¹⁷

The pharmacokinetic (PK) profiles of peficitinib and its key plasma metabolites (H1, H2 and H4, shown to have very weak pharmacological activity in a cell-based assay of T-cell proliferation)^{13,18} have been examined extensively under fasted and fed conditions (for single- and multiple-dose administration, respectively), in two phase I randomized, placebo-controlled studies in the US¹⁹ and a phase I randomized, placebo-controlled study in Japan; with significant differences in plasma concentrations observed between subjects of different ethnicities.^{16,17} In the latter study, $C_{\max}$ was 45.7–98.8% higher and AUC_{inf} was 33.8–66.4% higher in Japanese versus Caucasian subjects.¹⁶ Additionally, peficitinib was well tolerated and dose-proportional exposure was demonstrated in each study.

This study was performed to expand upon the PK profile and safety data for peficitinib after single- and multiple-dose administration of 50, 100, and 150 mg peficitinib in healthy Chinese subjects.

Methods

Ethics

The study was reviewed and approved by the Ethics Committee of Beijing Hospital (2019BJYYEC-093-01), and conducted in accordance with applicable Chinese/International Conference on Harmonization (ICH) Good Clinical Practices (GCP) guidelines, applicable regulations and guidelines governing clinical study conduct, the ethical principles that have their origin in the Declaration of Helsinki, and CIOMS International Ethical Guidelines. All subjects provided written informed consent before undergoing any study-related procedures.

Study Design

This was an open-label, randomized study, conducted between December 2019 and December 2020 at one site in China. The aim of this study was to investigate the PK profile and safety of peficitinib in healthy Chinese subjects after single and multiple doses of 50, 100, and 150 mg peficitinib, using 50 mg tablets.

Study Subjects

Eligible subjects were healthy Chinese male or female adults aged ≥ 18 –45 years, with a body mass index (BMI) $> 19 \text{ kg/m}^2$ and $\leq 24 \text{ kg/m}^2$, and a weight of $\geq 50 \text{ kg}$ for males and $\geq 45 \text{ kg}$ for females, at screening. Exclusion criteria included pregnancy (current or < 6 months prior to screening); hypersensitivity to peficitinib (or formulation) and liver chemistry tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT] and total bilirubin [TBL]) above the upper limit of normal on Day -1 .

Study Drug and Administration

Subjects were randomly allocated to one of three dose groups (50, 100, and 150 mg), with 6 male and 6 female subjects assigned to each group. Subjects were then sequentially enrolled into a single-dose period followed by a multiple-dose period. Study flow is described in Figure 1. On the morning of Day 1 (single-dose period), subjects were fasted for ≥ 10 hours prior to receiving a single oral dose of peficitinib with 150 mL warm water. Blood samples were collected immediately prior to administration and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours after administration of peficitinib.

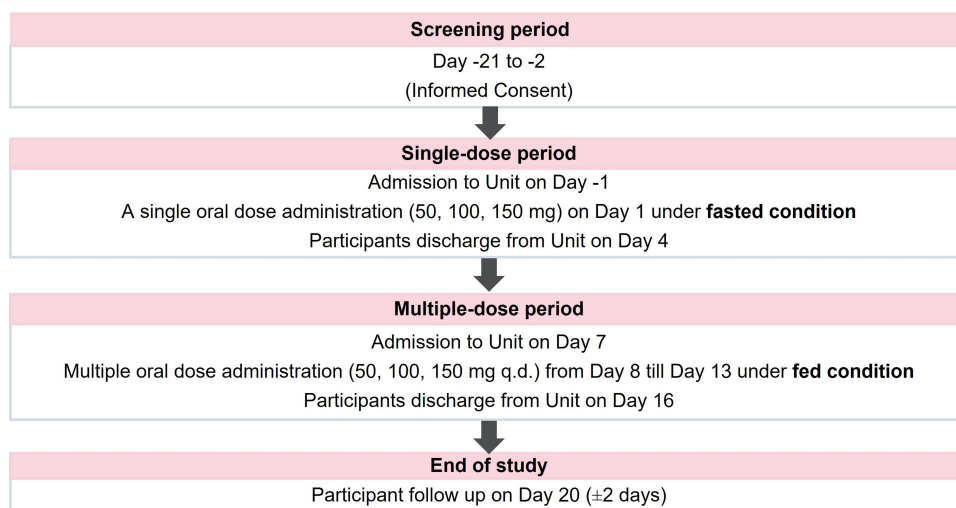


Figure 1 Study flow diagram.

The multiple-dose period was from Day 8 through Day 13, during which time subjects received peficitinib once daily, in the morning, for 6 consecutive days. On Days 8–13, subjects were fed in unison approximately 30 minutes prior to receiving a single oral dose of peficitinib with 150 mL warm water. Blood samples were collected immediately prior to administration on each day. Blood samples were also collected on Day 8, at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours after administration, and on Day 13, at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours after administration.

Physical examination, vital sign measurements, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations (including hematology, clinical chemistry, serology, urinalysis, and pregnancy test) were conducted at pre-specified times throughout the study at the local laboratory of the clinical center.

Sample Analyses for Peficitinib and Metabolites

Plasma concentrations of peficitinib and metabolite H4 were simultaneously measured using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Peficitinib, metabolite H4, and the internal standard (IS), which was stable isotope label ($[D_3]$ -peficitinib), were extracted by supported liquid extraction (SLE) using Isolute SLE+ 96-well plate (Biotage, Uppsala, Sweden), and separated by a column of BetaSil Silica, 5 μ m, 50 $\times$ 3.0 mm (Thermo Fisher Scientific, Waltham, MA, USA). Detection was performed via API5500 mass spectrometer (AB Sciex, Framingham, MA, USA) using positive Turbo ion spray ionization. The lower limit of quantification (LLOQ) was 0.25 ng/mL, when 70 μ L of plasma was used. Calibration curves for peficitinib and metabolite H4 in human plasma were linear over the concentration range 0.25–250 ng/mL. The inter-run accuracy of peficitinib and metabolite H4 varied between –2.3% and 4.1%, while the inter-run precision ranged between 2.8% and 4.9%.

Plasma concentrations of metabolites H1 and H2 were simultaneously measured using a validated LC-MS/MS method. Metabolites H1 and H2, and the ISs, which were stable isotope labels (metabolites $[D_3]$ -H1 and $[D_3]$ -H2), were extracted by protein precipitation and separated by a column of Acquity UPLC BEH Amide, 1.7 μ m, 100 $\times$ 2.1 mm (Waters, Milford, MA, USA). Detection was performed via API6500 mass spectrometer (AB Sciex) using positive Turbo ion spray ionization. The LLOQ was 0.25 ng/mL, when 50 μ L of human plasma was used. Calibration curves for metabolites H1 and H2 in plasma were linear over the concentration range 0.25–250 ng/mL. The inter-run accuracy of metabolites H1 and H2 varied between 2.5% and 4.7%, while the inter-run precision ranged between 3.4% and 5.6%.

Pharmacokinetic Assessments

The PK profile of peficitinib and its metabolites were assessed based on the following:

Plasma Peficitinib Concentration and PK Parameters

- Day 1 (single-dose): AUC_{inf} , AUC_{last} , AUC_{24h} , CL/F , C_{max} , $\lambda_{1/2}$, t_{max} , and V_z/F
- Day 8 (multiple-dose): AUC_{last} , AUC_{24h} , C_{max} , and t_{max}
- Day 9 through Day 12 (multiple-dose): C_{trough}
- Day 13 (multiple-dose): AUC_{24h} , CL/F , C_{trough} , C_{24h} , C_{max} , $\lambda_{1/2}$, t_{max} , peak-trough ratio (PTR), $R_{ac}(AUC_{24h})$, and $R_{ac}(C_{max})$

Plasma Metabolite (H1, H2 and H4) Concentrations and PK Parameters

- Day 1 (single-dose): AUC_{inf} , AUC_{last} , AUC_{24h} , C_{max} , $\lambda_{1/2}$, t_{max} , and metabolite/parent ratio (MPR)
- Day 8 (multiple-dose): AUC_{last} , AUC_{24h} , C_{max} , t_{max} , and MPR
- Day 9 through Day 12 (multiple-dose): C_{trough}
- Day 13 (multiple-dose): AUC_{24h} , C_{trough} , C_{24h} , C_{max} , $\lambda_{1/2}$, t_{max} , PTR, $R_{ac}(AUC_{24h})$, $R_{ac}(C_{max})$, and MPR

Safety Assessments

The incidence, nature, and severity of treatment-emergent adverse events (TEAEs), clinical laboratory tests (hematology, chemistry, urinalysis), vital signs, 12-lead ECG, and physical examination findings were evaluated throughout the study, to Day 20 $\pm$ 2. TEAEs were defined as any untoward medical occurrence in a subject following administration of the study drug that did not necessarily have a causal relationship with treatment.

Statistical Analyses

Planned Sample Size

The recommended population size for a PK study, according to National Medical Products Administration (NMPA) guidelines, is 8 to 12 subjects per dose group. In this study, a total of 36 healthy subjects (6 males and 6 females per 50, 100, and 150 mg dose groups) were planned to be enrolled to ensure a minimum of 24 subjects (4 males/4 females per dose group). No formal statistical sample size calculation was performed in this study.

Two analysis sets were included in this study: the safety analysis set (SAF), consisting of all subjects who received ≥ 1 dose of peficitinib; and the PK analysis set (PKAS), consisting of all subjects who received ≥ 1 dose of peficitinib and provided ≥ 1 estimable PK parameter.

Pharmacokinetic Analysis

Analyses performed on the PKAS were plasma concentrations and PK parameters for peficitinib and its metabolites, with data summarized descriptively at each time point.

PK parameters were calculated from plasma concentrations of peficitinib and its metabolites, and elapsed times from last dosing, using a non-compartmental analysis method. Half-life ($t_{1/2}$) was calculated from the slope of the elimination phase of the plasma concentration curve.

Dose proportionality was evaluated by C_{max} , AUC_{last} , and AUC_{inf} for single-dose administration (Day 1) and C_{max} and AUC_{24h} for multiple-dose administration (Day 13) using the following linearization of the power model:

$$\ln(\text{pharmacokinetic parameter}) = \beta_0 + \beta_1 \cdot \ln(\text{dose})$$

where β_0 was the intercept and β_1 was the slope. Dose proportionality was to be declared if the 90% confidence interval (CI) for β_1 lay entirely within the critical region ($1 + [\ln 0.5]/[\ln r]$, $1 + [\ln 2]/[\ln r]$), where r was the ratio of the highest and the lowest dose used in the model.

Gender differences were examined by treatment group for natural log-transformed C_{max} , AUC_{last} , and AUC_{inf} for single-dose administration (Day 1) and C_{max} and AUC_{24h} for multiple-dose administration (Day 13). Steady-state was assessed by visual inspection of line plots of individual and mean $\pm$ standard deviation (SD) C_{trough} of peficitinib and its metabolites from Day 9–13.

Safety Analysis

Safety analyses were performed on the SAF, and the proportions of subjects with TEAEs (including drug-related TEAEs and TEAEs leading to discontinuations) were summarized for single- and multiple-dose periods. Similarly, laboratory, vital sign and 12-lead ECG data (with change from baseline), were also summarized separately for both single- and multiple-dose periods. The proportion of normal/abnormal ECG data were shown for each time point in both single- and multiple-dose periods.

Results

Subject Dispositions

Overall 221 subjects provided informed consent, and 185 failed the screening procedure (subjects had clinically significant abnormalities, as determined by the investigator at screening or Day -1). In total, 36 subjects were enrolled and completed the study, with no discontinuations across the study period. Twelve subjects (6 males and 6 females) were assigned to each peficitinib dose group (50, 100, and 150 mg).

Subject Demographics and Baseline Characteristics

In accordance with the study protocol, 50% of subjects were male, with mean (SD) age 30.4 (7.71) years and mean (SD) BMI 21.5 (1.2) kg/m² at screening (Table 1). No subjects had high levels of substance abuse (≥ 10 cigarettes or ≥ 21 units of alcohol per day within 3 months prior to admission, or any prior history of drug abuse) (data not shown). Additionally, demographic and other baseline characteristics were similar between the peficitinib 50, 100, and 150 mg dose groups.

Table 1 Patient Demographics and Baseline Characteristics (SAF)

Parameter	Category/ Statistic	Peficitinib 50 mg (N=12)	Peficitinib 100 mg (N=12)	Peficitinib 150 mg (N=12)	Total (N=36)
Age (years) ^a	n	12	12	12	36
	Mean (SD)	34.0 (7.48)	25.6 (5.71)	31.6 (7.73)	30.4 (7.71)
	Min, Max	25, 45	20, 40	21, 43	20, 45
	Median	32.0	24.0	32.5	28.0
Sex, n (%)	Male	6 (50.0)	6 (50.0)	6 (50.0)	18 (50.0)
	Female	6 (50.0)	6 (50.0)	6 (50.0)	18 (50.0)
Race, n (%)	Asian	12 (100)	12 (100)	12 (100)	36 (100)
Country, n (%)	China	12 (100)	12 (100)	12 (100)	36 (100)
Height (cm)	Mean (SD)	161.8 (7.1)	163.5 (9.7)	161.0 (4.6)	162.1 (7.3)
	Min, Max	151.4, 170.5	148.9, 178.2	152.6, 168.9	148.9, 178.2
	Median	162.60	166.10	160.80	161.40
Weight (kg)	Mean (SD)	56.4 (4.8)	57.5 (5.1)	55.6 (4.7)	56.5 (4.8)
	Min, Max	47.4, 62.4	50.0, 67.2	48.5, 62.6	47.4, 67.2
	Median	57.90	57.65	56.40	57.65
BMI (kg/m ²)	Mean (SD)	21.5 (1.2)	21.5 (1.3)	21.4 (1.2)	21.5 (1.2)
	Min, Max	19.7, 23.4	19.2, 23.1	19.8, 23.4	19.2, 23.4
	Median	21.60	22.15	21.15	21.50

Notes: ^aCalculated at the time of informed consent. Weight at screening; Height at screening; BMI at screening, calculated as weight/(height²). Baseline is the last non-missing measurement prior to initial dosing of study drug.

Abbreviations: SAF, safety analysis set; BMI, body mass index.

Pharmacokinetics

Peficitinib Plasma Concentration and PK Parameters

In the single-dose period (Day 1), peficitinib demonstrated rapid absorption with a median $t_{\max}$ of 1.0–1.5 hours after administration (fasted state), and plasma levels declined with a mean $t_{1/2}$: 7.4–13.0 hours across all dose groups (Table 2). Peficitinib also showed a V_z/F of 718–1548 L across all dose groups with high variability (coefficient of variation, $CV > 59\%$). In the multiple-dose period (Days 8–13), median $t_{\max}$ was delayed versus the single-dose period, ranging from 1.5–2.0 hours after peficitinib administration (fed state). Peficitinib showed no accumulation by Day 13, with ratios $R_{ac}[AUC_{24h}]$ and $R_{ac}[C_{\max}]$ close to 1. Mean trough plasma peficitinib concentrations showed a slight increase towards Day 13, with steady state achieved by Day 11 (Supplementary Figure 1).

In both single- and multiple-dose periods, a dose-proportional increase in $C_{\max}$ and AUC_{24h} was observed across all peficitinib dose groups (Supplementary Table 1), with moderate to low variability (CV 14.8–38.7%) (Table 2). Mean concentration-time profiles of peficitinib on Day 1, Day 8, and Day 13 are shown in Figure 2.

Peficitinib Metabolite (H1, H2 and H4) Plasma Concentration and PK Parameters

In both single- and multiple-dose periods, the median $t_{\max}$ for metabolite formation was 3 hours each for H1 and H4, and 2 hours for H2, with a mean $t_{1/2}$ of 5.3–13.7 hours across all peficitinib dose groups (Table 3). For each metabolite, a dose-proportional increase in $C_{\max}$ and AUC_{24h} was observed in both single- and multiple-dose periods and across all dose groups (Supplementary Table 1), with minimal to no accumulation ($R_{ac}[AUC_{24h}]$ and $R_{ac}[C_{\max}]$ of 0.81–1.15 hours).

For metabolite H2, the MPR ranged from 1.52–1.93 indicating systematic exposure of $>150\%$ for peficitinib AUC across all peficitinib dose groups (Table 3). However, neither metabolite H1 nor H4 demonstrated MPR exceeding 0.3 in either the single- or multiple-dose periods.

In the multiple-dose period, mean trough concentrations of each metabolite increased from Day 9 until Day 10, with steady state achieved by Day 11 at the latest across almost all peficitinib dose groups (Supplementary Figures 2–4). Mean concentration-time profiles of each metabolite (H1, H2 and H4) on Day 1, Day 8, and Day 13 are shown in Figure 3.

Gender Analysis

There were no meaningful gender differences observed in the peficitinib or metabolite H2 PK profiles in either the single- or multiple-dose periods, with $GMR_{\text{female/male}}$ of 79.7–134.1% and 78.4–129.5%, respectively (Supplementary Table 2).

For metabolites H1 and H4, a higher exposure was observed in females than males following single-dose and multiple-dose administration of peficitinib across all doses, with $GMR_{\text{female/male}}$ of 124.6–185.8% and 112.1–207.6%, respectively.

Safety

Adverse Events

In the single-dose period, 6 (16.7%) subjects experienced 12 TEAEs, of whom 5 (13.9%) subjects experienced 9 TEAEs considered to be drug related (Table 4). The most frequent drug-related TEAEs were headaches (2 events in 2 [5.6%] subjects) and coughs (2 events in 2 [5.6%] subjects) (Table 5).

In the multiple-dose period, 12 (33.3%) subjects experienced 24 TEAEs, of which 22 TEAEs were considered to be drug-related. TEAEs occurred more frequently for peficitinib 100 and 150 mg dose groups than for peficitinib 50 mg, and were recorded in 4 (33.3%), 7 (58.3%), and 1 (8.3%) subjects, respectively (Table 4). The most frequent drug-related TEAEs were nausea (5 events in 5 [13.9%] subjects), dizziness (4 events in 2 [5.6%] subjects), increased blood cholesterol (2 events in 2 [5.6%] subjects), dyspepsia (3 events in 2 [5.6%] subjects) and arthralgia (2 events in 2 [5.6%] subjects) (Table 5).

All TEAEs were mild in severity, with no deaths, severe adverse events or TEAEs leading to discontinuation in this study.

Laboratory Parameters

Overall, five subjects recorded clinically significant abnormalities from clinical laboratory evaluations, vital signs, physical examination, 12-lead ECG or chest X-ray in this study. However, no clinically meaningful findings related to

Table 2 Peficitinib Pharmacokinetic Parameters (PKAS)

Parameter	Statistic	Day 1			Day 8			Day 13		
		Peficitinib 50 mg Fasted (N=12)	Peficitinib 100 mg Fasted (N=12)	Peficitinib 150 mg Fasted (N=12)	Peficitinib 50 mg Fed (N=12)	Peficitinib 100 mg Fed (N=12) ^a	Peficitinib 150 mg Fed (N=12)	Peficitinib 50 mg Fed (N=12)	Peficitinib 100 mg Fed (N=12) ^a	Peficitinib 150 mg Fed (N=12)
C _{max} (ng/mL)	Mean (SD)	237.6 (58.05)	399.0 (98.58)	620.1 (240.3)	227.1 (80.51)	478.5 (109.3)	723.7 (245.5)	257.6 (55.41)	510.5 (86.57)	743.3 (208.4)
	%CV	24.4	24.7	38.7	35.4	22.8	33.9	21.5	17.0	28.0
t _{max} (h)	Median	1.250	1.500	1.000	1.750	2.000	1.500	1.500	2.000	1.750
t _{1/2} (h)	Mean (SD)	7.375 (5.392)	13.01 (8.285)	11.32 (7.273)	NC			8.646 (6.437)	9.964 (5.181)	12.49 (8.271)
	%CV	73.1	63.7	64.2				74.5	52.0	66.2
AUC _{24h} (h*ng/mL)	Mean (SD)	725.4 (143.0)	1287 (303.8)	1814 (498.7)	718.0 (172.6)	1448 (284.2)	2191 (530.0)	822.9 (148.8)	1633 (242.5)	2496 (561.1)
	%CV	19.7	23.6	27.5	24.0	19.6	24.2	18.1	14.8	22.5
V _z /F (L)	Mean (SD)	718.3 (509.8)	1548 (1143)	1312 (780.4)	NC					
	%CV	71.0	73.8	59.5						
R _{ac} (AUC _{24h})	Mean (SD)	NC						1.169 (0.1242)	1.141 (0.1011)	1.153 (0.1517)
	%CV							10.6	8.9	13.2
R _{ac} (C _{max})	Mean (SD)	NC						1.203 (0.2824)	1.100 (0.2233)	1.059 (0.1674)
	%CV							23.5	20.3	15.8

Note: ^aConcentration data of one subject was excluded from summary statistics due to implausible low concentrations based on pharmacokinetic profile.

Abbreviations: AUC_{24h}, area under the concentration-time curve from the time of dosing to 24 hours postdose; C_{max}, maximum concentration; NC, parameters not calculated; PKAS, pharmacokinetic analysis set; R_{ac}, accumulation ratio; t_{max}, time of maximum concentration; t_{1/2}, terminal elimination half-life; V_z/F, apparent volume of distribution during the terminal elimination phase after single extravascular dosing.

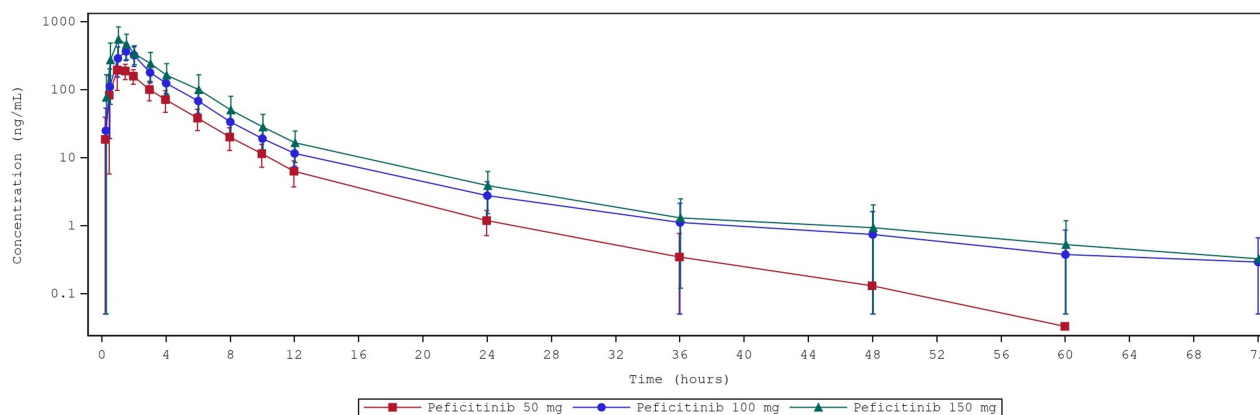
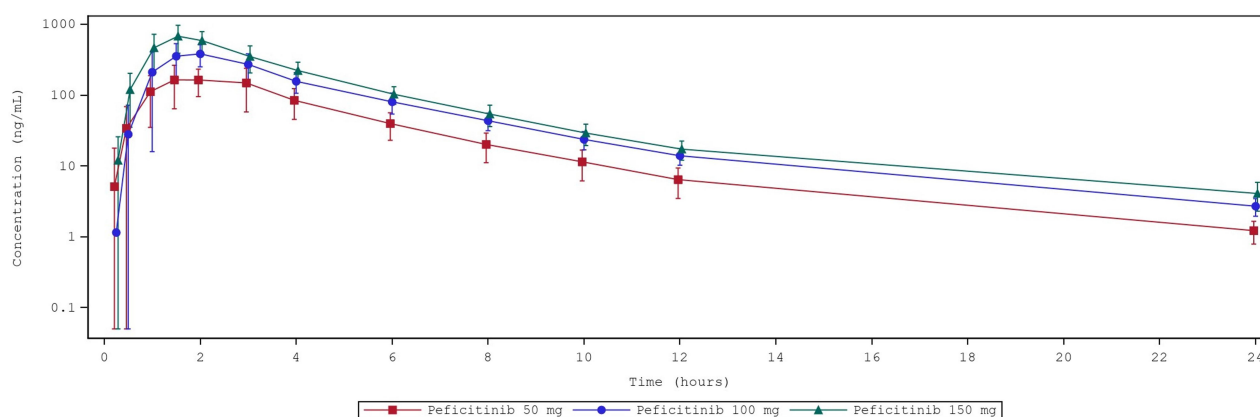
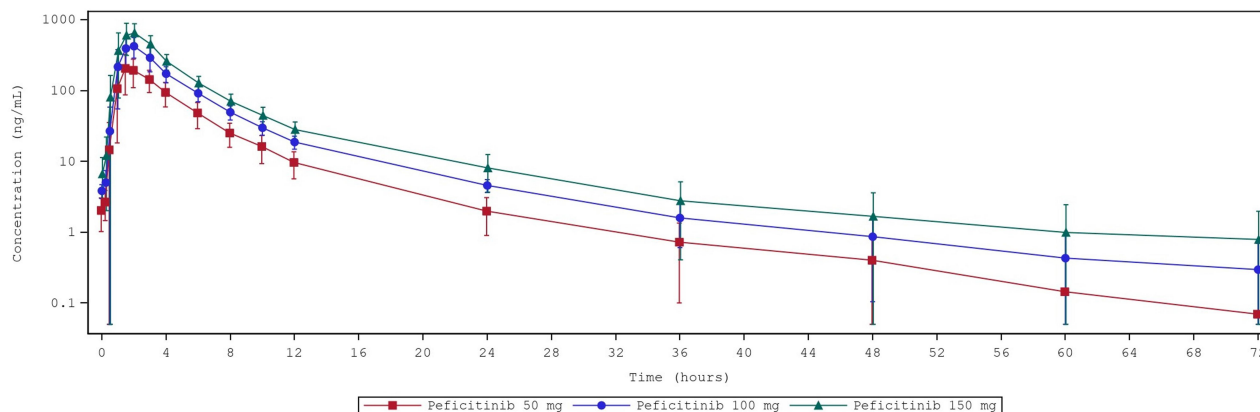
Day 1**Day 8****Day 13**

Figure 2 Mean ($\pm$ SD) concentration-time profiles of peficitinib on Day 1, Day 8, and Day 13 (PKAS). SD was not calculated since >50% of values were below the quantitation limit at a given time point.

peficitinib were identified in the single-dose period. Three subjects with increased cholesterol or bilirubin were identified from clinical chemistry evaluations in the multiple-dose period, which were considered possibly or probably related to peficitinib ([Supplementary Table 3](#)).

Discussion

Ethnicity has been previously shown to be responsible for variability in the pharmacokinetics and pharmacodynamics of drugs, which can lead to alterations in their safety and efficacy.²⁰ As a result, the PK profile of peficitinib has been well

Table 3 Peficitinib Metabolite Pharmacokinetic Parameters (SAF)

Parameter	Statistic	Day 1			Day 8			Day 13		
		Peficitinib 50 mg Fasted (N=12)	Peficitinib 100 mg Fasted (N=12)	Peficitinib 150 mg Fasted (N=12)	Peficitinib 50 mg Fed (N=12)	Peficitinib 100 mg Fed (N=12) ^a	Peficitinib 150 mg Fed (N=12)	Peficitinib 50 mg Fed (N=12)	Peficitinib 100 mg Fed (N=12) ^a	Peficitinib 150 mg Fed (N=12)
Metabolite H1										
C _{max} (ng/mL)	Mean (SD) %CV	31.39 (15.32) 48.8	51.37 (21.13) 41.1	66.30 (30.91) 46.6	45.51 (21.60) 47.5	54.51 (19.18) 35.2	80.61 (39.78) 49.4	34.04 (15.89) 46.7	48.89 (17.42) 35.6	64.47 (32.88) 51.0
t _{max} (h)	Median	2.000	3.000	2.000	3.000	3.000	3.000	3.000	3.000	3.000
t _{1/2} (h)	Mean (SD) %CV	5.261 (0.7869) 15.0	9.102 (5.574) 61.2	12.58 (8.725) 69.4	NC			7.755 (3.550) 45.8	11.29 (5.824) 51.6	12.28 (7.084) 57.7
AUC _{24h} (h*ng/mL)	Mean (SD) %CV	209.0 (60.27) 28.8	326.4 (123.5) 37.8	447.9 (202.2) 45.1	248.3 (69.05) 27.8	336.1 (120.6) 35.9	515.3 (222.7) 43.2	222.0 (64.07) 28.9	334.0 (119.4) 35.7	469.9 (222.0) 47.2
MPR	Mean (SD) %CV	0.2311 (0.07275) 31.5	0.2110 (0.09795) 46.4	0.2076 (0.1024) 49.3	0.3019 (0.1948) 64.5	0.1837 (0.07461) 40.6	0.1870 (0.07828) 41.9	0.2251 (0.08904) 39.6	0.1636 (0.05512) 33.7	0.1575 (0.07288) 46.3
R _{ac} (AUC _{24h})	Mean (SD) %CV	NC						0.9083 (0.1668) 18.4	1.002 (0.1441) 14.4	0.9157 (0.1240) 13.5
R _{ac} (C _{max})	Mean (SD) %CV	NC						0.8122 (0.2457) 30.2	0.9108 (0.1786) 19.6	0.8117 (0.1178) 14.5
Metabolite H2										
C _{max} (ng/mL)	Mean (SD) %CV	510.9 (134.7) 26.4	756.0 (271.3) 35.9	1111 (348.3) 31.4	503.5 (209.4) 41.6	837.8 (271.9) 32.5	1424 (480.2) 33.7	516.8 (141.8) 27.4	917.3 (285.6) 31.1	1439 (450.1) 31.3
t _{max} (h)	Median	1.500	1.750	1.500	2.000	2.000	1.500	2.000	2.000	2.000
t _{1/2} (h)	Mean (SD) %CV	9.882 (5.668) 57.7	13.67 (7.330) 53.6	12.41 (8.367) 67.4	NC			9.161 (6.624) 72.3	12.29 (6.617) 53.8	13.25 (8.094) 61.1
AUC _{24h} (h*ng/mL)	Mean (SD) %CV	1692 (426.4) 25.2	2526 (818.9) 32.4	3729 (908.7) 24.4	1614 (497.7) 30.8	2786 (877.7) 31.5	4584 (1330) 29.0	1778 (441.8) 24.8	3112 (885.9) 28.5	5194 (1351) 26.0

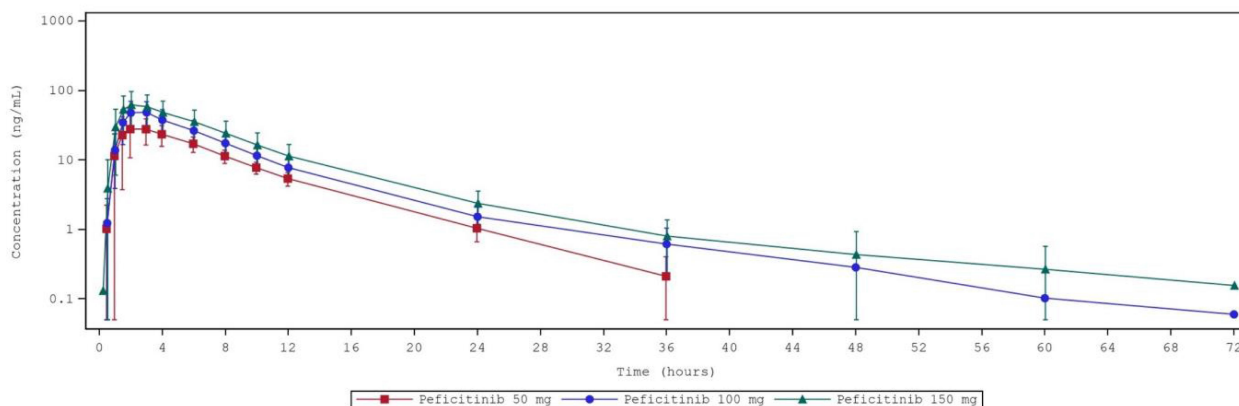
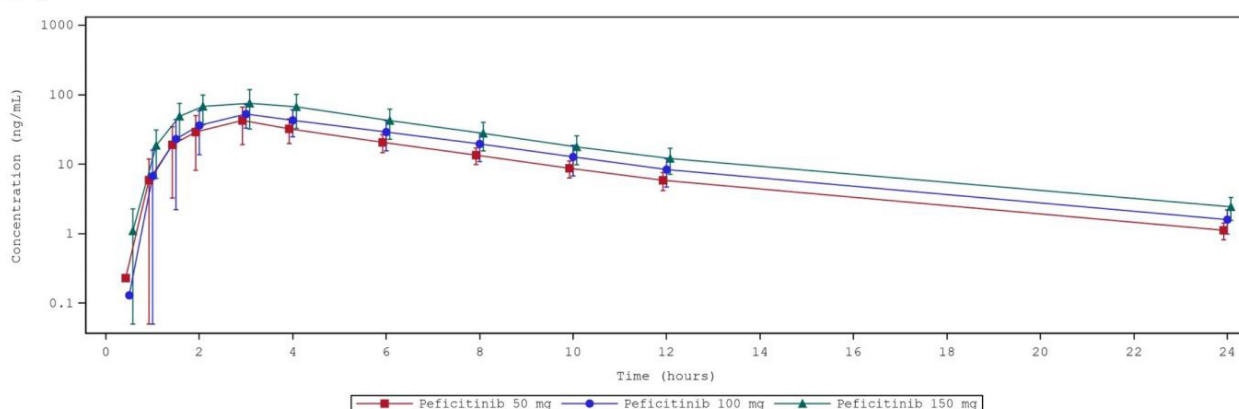
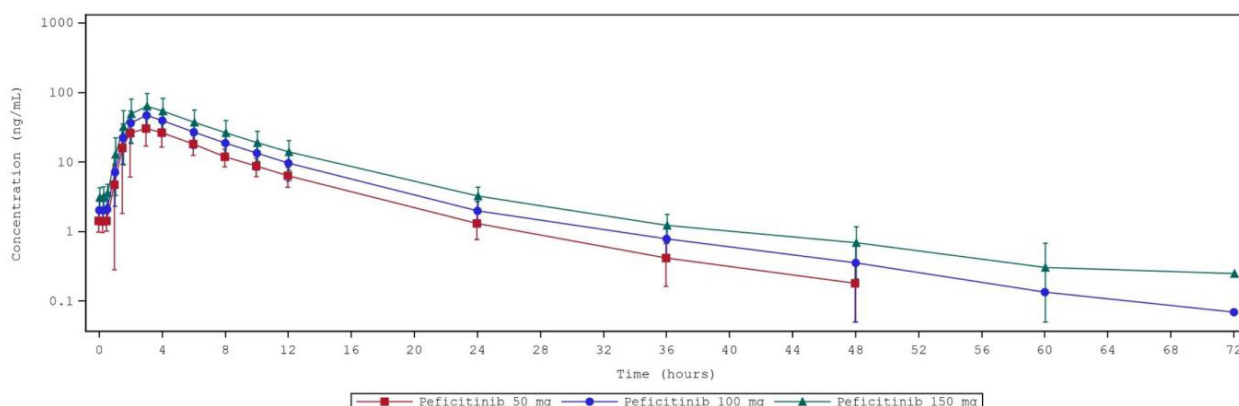
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Table 3 (Continued).

Parameter	Statistic	Day 1			Day 8			Day 13		
		Peficitinib 50 mg Fasted (N=12)	Peficitinib 100 mg Fasted (N=12)	Peficitinib 150 mg Fasted (N=12)	Peficitinib 50 mg Fed (N=12)	Peficitinib 100 mg Fed (N=12) ^a	Peficitinib 150 mg Fed (N=12)	Peficitinib 50 mg Fed (N=12)	Peficitinib 100 mg Fed (N=12) ^a	Peficitinib 150 mg Fed (N=12)
MPR	Mean (SD) %CV	1.927 (0.4979) 25.8	1.572 (0.2428) 15.4	1.729 (0.4764) 27.5	1.811 (0.4394) 24.3	1.524 (0.2436) 16.0	1.678 (0.4005) 23.9	1.759 (0.3982) 22.6	1.518 (0.2734) 18.0	1.682 (0.4063) 24.2
R _{ac} (AUC _{24h})	Mean (SD) %CV	NC						1.140 (0.1646) 14.4	1.132 (0.1291) 11.4	1.152 (0.1432) 12.4
R _{ac} (C _{max})	Mean (SD) %CV	NC						1.124 (0.3169) 28.2	1.115 (0.2043) 18.3	1.042 (0.1600) 15.4
Metabolite H4										
C _{max} (ng/mL)	Mean (SD) %CV	24.05 (8.542) 35.5	41.43 (13.34) 32.2	53.62 (23.21) 43.3	33.16 (14.89) 44.9	46.52 (14.87) 32.0	67.41 (29.42) 43.6	27.92 (9.038) 32.4	44.51 (11.98) 26.9	60.71 (27.92) 46.0
t _{max} (h)	Median	3.500	3.000	2.000	3.000	3.000	2.000	4.000	3.000	3.000
t _{1/2} (h)	Mean (SD) %CV	5.256 (0.9698) 18.5	9.747 (6.486) 66.5	11.63 (7.498) 64.5	NC			7.302 (3.750) 51.4	12.72 (4.888) 38.4	14.96 (6.214) 41.6
AUC _{24h} (h*ng/mL)	Mean (SD) %CV	189.0 (51.85) 27.4	324.1 (82.83) 25.6	423.1 (168.4) 39.8	206.8 (40.12) 19.4	346.8 (88.90) 25.6	479.9 (160.5) 33.4	210.9 (44.31) 21.0	360.7 (89.39) 24.8	504.1 (174.8) 34.7
MPR	Mean (SD) %CV	0.2517 (0.04260) 16.9	0.2589 (0.08559) 33.1	0.2298 (0.06926) 30.1	0.2954 (0.1173) 39.7	0.2336 (0.06094) 26.1	0.2159 (0.06252) 29.0	0.2565 (0.05653) 22.0	0.2220 (0.05410) 24.4	0.2092 (0.06452) 30.8
R _{ac} (AUC _{24h})	Mean (SD) %CV	NC						1.023 (0.1238) 12.1	1.047 (0.1084) 10.4	1.054 (0.1462) 13.9
R _{ac} (C _{max})	Mean (SD) %CV	NC						0.9069 (0.2274) 25.1	0.9800 (0.1467) 15.0	0.9051 (0.1736) 19.2

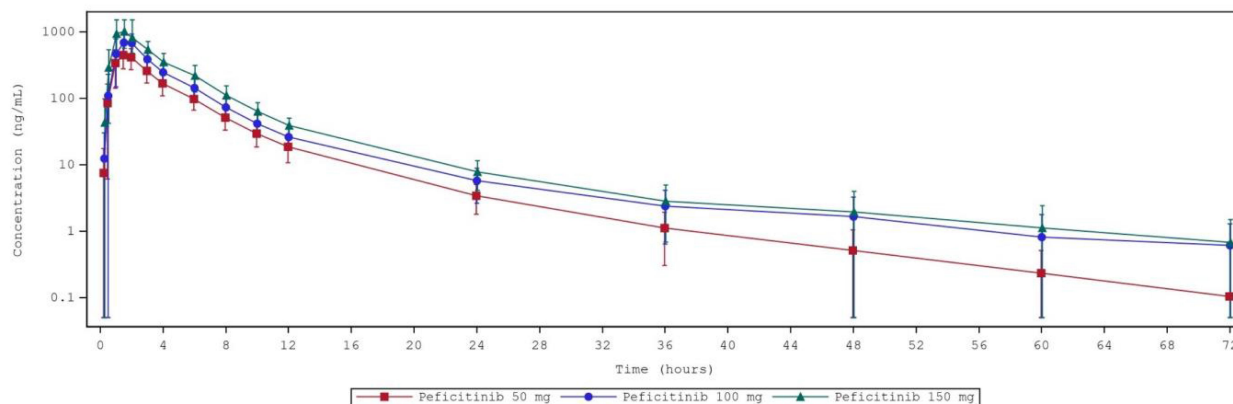
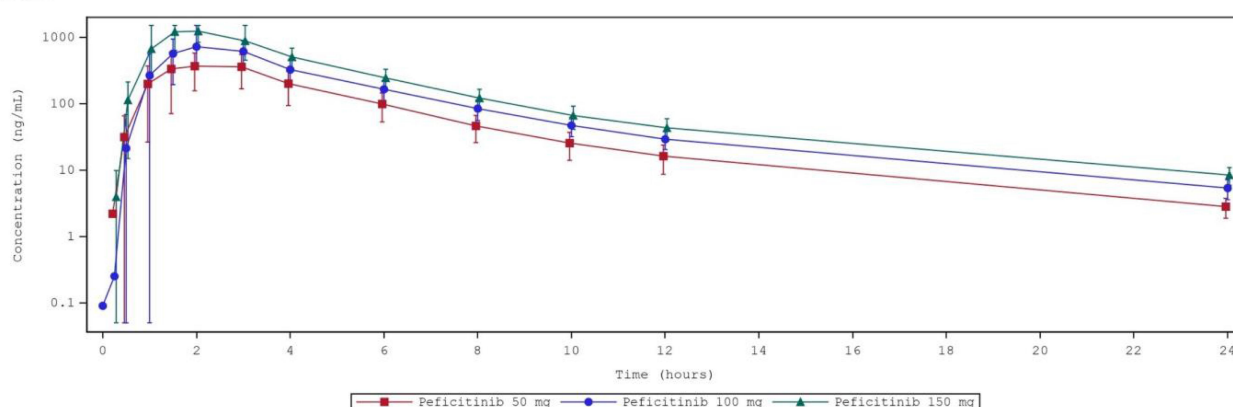
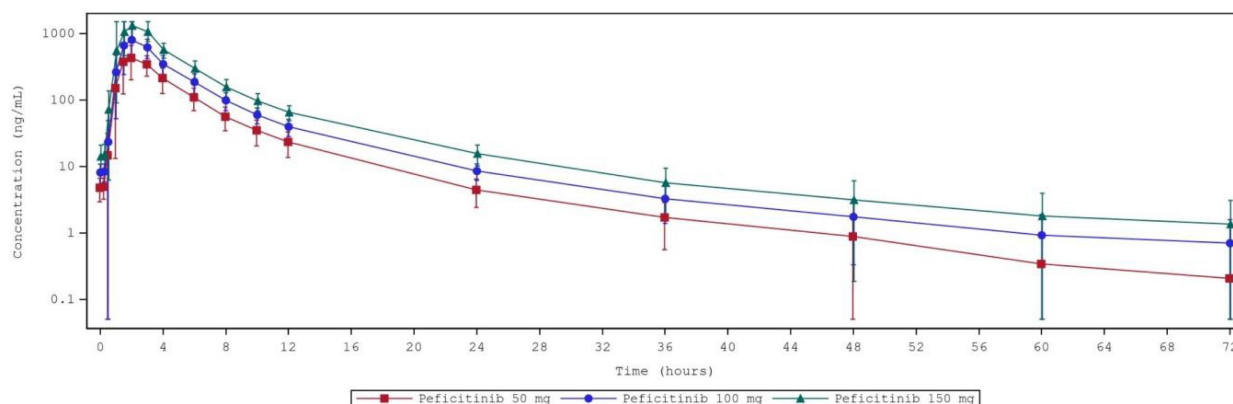
Note: ^aConcentration data of one subject was excluded from summary statistics due to implausible low concentrations based on pharmacokinetic profile.

Abbreviations: AUC_{24h}, area under the concentration-time curve from the time of dosing to 24 hours postdose; C_{max}, maximum concentration; MPR, metabolite to parent ratio; NC, parameters not calculated; PKAS, pharmacokinetic analysis set; R_{ac}, accumulation ratio; t_{max}, time of maximum concentration; t_{1/2}, terminal elimination half-life.

A**Day 1****Day 8****Day 13****Figure 3 Continued.**

explored in the Caucasian and Japanese populations.^{16–19,21} In this study, the PK profile of peficitinib was investigated extensively in 36 healthy Chinese subjects.

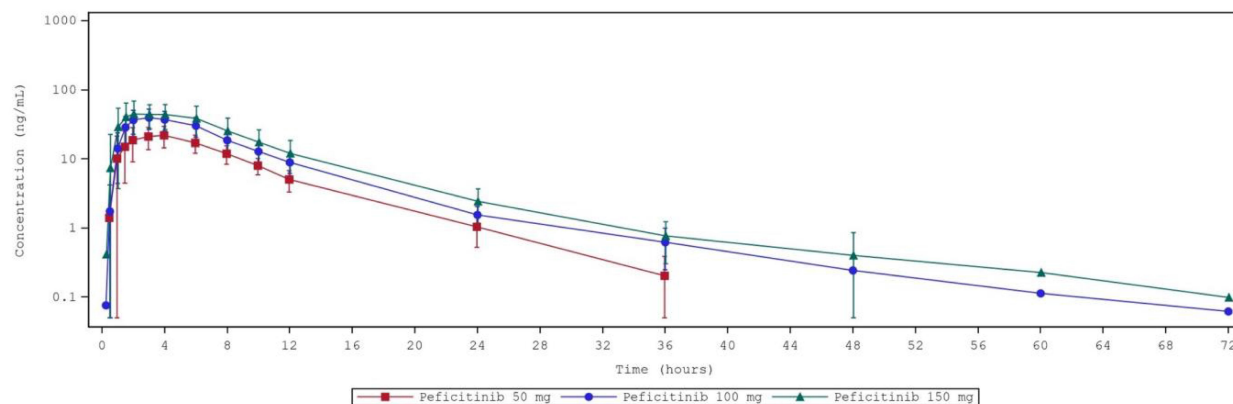
In this study, peficitinib demonstrated rapid absorption after single-dose administration with a median t_{max} of 1.0–1.5 hours (fasted state), which was slightly delayed to 1.5–2.0 hours following multiple-dose administration (fed state). This is supported by a previous study in healthy Japanese subjects, in which a single dose of peficitinib 150 mg was rapidly absorbed with a mean t_{max} of 1.6 hours in the fasted state, extending to 2.0 hours in the fed state.¹⁷ Elimination of peficitinib from blood plasma after both single- and multiple-dose administration at all dose levels in our study (mean $t_{1/2}$ 7.4–13.0 hours) was similar

B**Day 1****Day 8****Day 13****Figure 3** Continued.

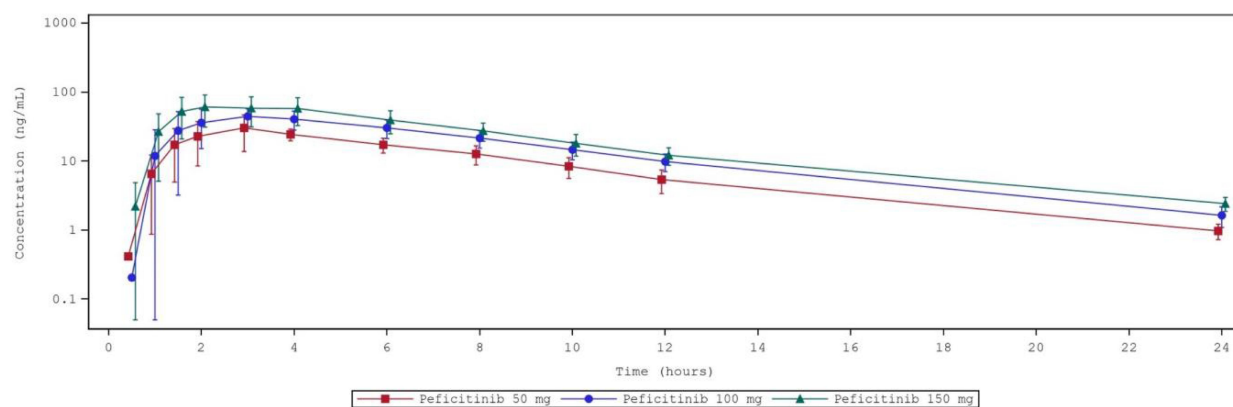
to that observed after single-dose administration of peficitinib 200 mg (mean $t_{1/2}$ 7.7–12.9 hours) in healthy Caucasian subjects.¹⁹ Studies in healthy Caucasian and Japanese subjects have also demonstrated similar mean t_{max} after both single- and multiple-dose administration of peficitinib.^{16,18,19,21} Additionally, although $t_{1/2}$ in this study had high variability, this trend has also been observed between related PK studies. Cao et al, reported $t_{1/2}$ of 14.2 (± 8.9) hours and 17.7 (± 9.4) hours following multiple-dose administration of peficitinib 100 mg for male and female subjects respectively;¹⁹ Shibata et al, reported $t_{1/2}$ of

C

Day 1



Day 8



Day 13

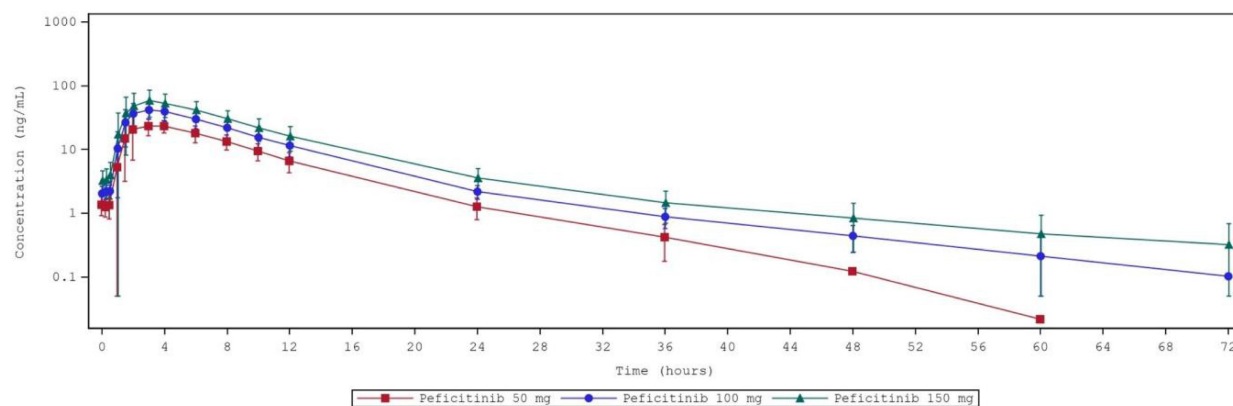


Figure 3 Mean ($\pm$ SD) concentration-time profiles of peficitinib metabolites on Day 1, Day 8, and Day 13 (PKAS). (A) H1; (B) H2; (C) H4. SD was not calculated since >50% of values were below the quantitation limit at a given time point.

12.0 ($\pm$ 11.3) hours and 9.3 ($\pm$ 7.8) hours following single dose administration of peficitinib 150 mg for fasted and fed subjects respectively.¹⁷

Dose-proportional increases in $C_{\max}$ and AUC_{24h} were observed in the present study for peficitinib and its metabolites, and across all peficitinib dose groups, with minimal or no accumulation. Since $t_{1/2}$ was also short at all dose levels, the influence of half-life to clinical efficacy was considered to be minor. Clear dose-proportional increases in peficitinib plasma concentration were also observed in studies of healthy Japanese and Caucasian subjects after single-dose administration.¹⁶

Table 4 Summary of Adverse Events for Single- and Multiple-Dose Periods (SAF)

Dosing Period	Peficitinib 50 mg (N=12) n (%)	Peficitinib 100 mg (N=12) n (%)	Peficitinib 150 mg (N=12) n (%)	Total (N=36) n (%)
Single-Dose Period				
AE	2 (16.7)	0	4 (33.3)	6 (16.7)
Drug-related ^a AE	2 (16.7)	0	3 (25.0)	5 (13.9)
Deaths	0	0	0	0
SAE	0	0	0	0
Drug-related ^a SAE	0	0	0	0
AE leading to discontinuation	0	0	0	0
Severe AE	0	0	0	0
Multiple-Dose Period				
AE	1 (8.3)	4 (33.3)	7 (58.3)	12 (33.3)
Drug-related ^a AE	1 (8.3)	4 (33.3)	7 (58.3)	12 (33.3)
Deaths	0	0	0	0
SAE	0	0	0	0
Drug-related ^a SAE	0	0	0	0
AE leading to discontinuation	0	0	0	0
Severe AE	0	0	0	0

Notes: ^aRelationships including 'not related', 'possibly related', 'probably related' or 'unknown', were assessed by the investigator. Drug-related AE was considered if relationship of any AE was classified as 'possibly related', 'probably related', or 'unknown'. Events with missing or unknown relationship were considered as 'related' but recorded as missing in the listings. All AEs occurred after the first single dose of study drug and were regarded as TEAEs.

Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event. n (%) represented number and percent of subjects with events.

In general, exposure to peficitinib was higher for multiple- versus single-dose administration (excluding the 50 mg dose group on Day 1 versus Day 8), with low variability in both groups. Metabolites H1 and H4 were minor metabolites, with relative systemic exposures <30% of the parent peficitinib (MPR <0.3). However, metabolite H2 was a major metabolite, with a relative systemic exposure of >150% (MPR >1.5) of the parent peficitinib AUC values. This is supported by single dose peficitinib studies in healthy Japanese subjects, which showed similar MPRs for metabolites H1 and H4, and MPR >1.8 for H2.^{18,21} However, since the pharmacological activity of metabolites H1, H2 and H4 were very weak, and the active form in vivo is peficitinib,¹³ exposure of those metabolites was considered to be of no clinical significance.

The impact of gender has been examined previously in healthy Caucasian subjects, with negligible effect observed on pharmacokinetics, pharmacodynamics or safety profiles after either single or multiple doses of peficitinib.¹⁹ Similarly, for Chinese subjects in the current study, no marked gender differences were observed in PK parameters after single- and multiple-dose administration of peficitinib across all doses studied.

Overall, peficitinib was well tolerated in Chinese subjects at all doses in the study. Although TEAEs were observed to occur more frequently in higher than lower dose groups, all TEAEs were mild in severity, with no deaths or TEAEs that led to discontinuation. Following single-dose administration of peficitinib, five subjects recorded TEAEs considered to be drug related by the investigator (most frequently headaches and coughs). Following multiple-dose administration of peficitinib, 12 subjects reported TEAEs considered to be drug-related (primarily nausea, increased blood cholesterol, dyspepsia and arthralgia). Decreased neutrophil counts reported in similar studies in healthy Caucasian and Japanese subjects^{16,19} were not observed in this study. Additionally, no new clinically meaningful abnormal laboratory findings were identified after single-dose administration.

Limitations of this study include the short study duration. Since RA is a chronic disease, peficitinib is typically administered for extended periods, therefore long-term safety assessments would be of greater clinical relevance for Chinese patients. Additionally, these data are restricted to healthy individuals who are relatively young. This is not necessarily representative of the age demographic for the RA patient population in which peficitinib is indicated, many of whom have also comorbidities and are receiving concomitant medications.¹⁹ Primary strengths of this study include

Table 5 Drug-Related TEAEs During the Single and Multiple-Dose Periods (SAF)

System Organ Class PT (MedDRA v23.0)	Peficitinib 50 mg (N=12) n (%) #E	Peficitinib 100 mg (N=12) n (%) #E	Peficitinib 150 mg (N=12) n (%) #E	Total (N=36) n (%) #E
Single-dose Period				
Overall	2 (16.7) 2	0	3 (25.0) 7	5 (13.9) 9
Gastrointestinal disorders	0	0	1 (8.3) 1	1 (2.8) 1
Nausea	0	0	1 (8.3) 1	1 (2.8) 1
Infections and infestations	1 (8.3) 1	0	0	1 (2.8) 1
Upper respiratory tract infection	1 (8.3) 1	0	0	1 (2.8) 1
Nervous system disorders	1 (8.3) 1	0	1 (8.3) 1	2 (5.6) 2
Headache	1 (8.3) 1	0	1 (8.3) 1	2 (5.6) 2
Respiratory, thoracic and mediastinal disorders	0	0	3 (25.0) 5	3 (8.3) 5
Cough	0	0	2 (16.7) 2	2 (5.6) 2
Oropharyngeal discomfort	0	0	1 (8.3) 1	1 (2.8) 1
Oropharyngeal pain	0	0	1 (8.3) 1	1 (2.8) 1
Throat irritation	0	0	1 (8.3) 1	1 (2.8) 1
Multiple-dose Period				
Overall	1 (8.3) 1	4 (33.3) 9	7 (58.3) 12	12 (33.3) 22
Ear and labyrinth disorders	0	0	1 (8.3) 1	1 (2.8) 1
Tinnitus	0	0	1 (8.3) 1	1 (2.8) 1
Gastrointestinal disorders	0	2 (16.7) 4	3 (25.0) 5	5 (13.9) 9
Nausea	0	2 (16.7) 2	3 (25.0) 3	5 (13.9) 5
Dyspepsia	0	1 (8.3) 2	1 (8.3) 1	2 (5.6) 3
Abdominal pain upper	0	0	1 (8.3) 1	1 (2.8) 1
General disorders and administration site conditions	0	1 (8.3) 1	0	1 (2.8) 1
Fatigue	0	1 (8.3) 1	0	1 (2.8) 1
Investigations	1 (8.3) 1	1 (8.3) 1	1 (8.3) 1	3 (8.3) 3
Blood cholesterol increased	1 (8.3) 1	1 (8.3) 1	0	2 (5.6) 2
Blood bilirubin increased	0	0	1 (8.3) 1	1 (2.8) 1
Musculoskeletal and connective tissue disorders	0	0	2 (16.7) 2	2 (5.6) 2
Arthralgia	0	0	2 (16.7) 2	2 (5.6) 2
Nervous system disorders	0	2 (16.7) 3	1 (8.3) 2	3 (8.3) 5
Dizziness	0	1 (8.3) 2	1 (8.3) 2	2 (5.6) 4
Somnolence	0	1 (8.3) 1	0	1 (2.8) 1
Respiratory, thoracic and mediastinal disorders	0	0	1 (8.3) 1	1 (2.8) 1
Oropharyngeal pain	0	0	1 (8.3) 1	1 (2.8) 1

Notes: Sorting order: ascending order by SOC code and descending by the number of subjects of total group by PT. In case of ties, ascending order by PT code was applied.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class. Number of subjects (n), percentage of subjects (%) and number of events (#E) were shown.

a study population comprised of both male and female subjects; PK studies commonly have only male subjects. Also, this was the first study to assess the PK profile of peficitinib in Chinese subjects. A further study is also currently ongoing (NCT03660059) investigating the safety and efficacy of peficitinib in patients with RA and an inadequate response to methotrexate in China.

In this study of peficitinib in healthy subjects in China, peficitinib was rapidly absorbed with plasma concentration varying in a dose-dependent manner, for both single- and multiple-dose administration. Several PK parameters (median $t_{\max}$, $t_{1/2}$, and dose-proportional increases in $C_{\max}$ and AUC_{24h}) for single and multiple doses of peficitinib 50, 100, and 150 mg were similar to those reported for Caucasian and Japanese subjects in previous studies. Peficitinib was well tolerated at all doses in the study.

Data Sharing Statement

Researchers may request access to anonymized participant level data, trial level data, and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx>.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

DM, HO, YO, YK, KK and TW are employees of Astellas Pharma Inc. CC and NS are employees of Astellas Pharma China, Inc. AS, XG and XH have nothing to disclose. The authors report no other conflicts of interest in this work.

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