The Bioequivalence of Two Peficitinib Formulations, and the Effect of Food on the Pharmacokinetics of Peficitinib: Two-Way Crossover Studies of a Single Dose of 150 mg Peficitinib in Healthy Volunteers

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Abstract

The marketed tablet formulation of peficitinib differs from the tablet used during the clinical trials. The bioequivalence of the marketed formulation and developmental tablet, and the food effect on the marketed formulation, were analyzed in 2 Japanese open-label, randomized, 2-way crossover studies in healthy male volunteers. Volunteers received a single oral dose of the marketed 150-mg peficitinib tablet under fasted conditions (bioequivalence), and under fed or fasted conditions (food effect). Bioequivalence was compared with the developmental 150-mg tablet. Samples for pharmacokinetic analysis were collected before dose and $\leq$72 hours after dose. Safety assessments included adverse events, vital signs, and laboratory variables. In total, 40 and 18 subjects were randomized to the bioequivalence and food effect studies, respectively. The 2 peficitinib formulations were bioequivalent (90% confidence intervals of the geometric mean ratios for C_{max} and AUC_t of peficitinib were within predefined limits of 0.8 to 1.25). The AUC_{last} and the C_{max} of the marketed tablet were 36.8% and 56.4% higher, respectively, under fed versus fasted conditions. Peficitinib was well tolerated. The marketed 150-mg tablet formulation of peficitinib was bioequivalent to the developmental 150-mg formulation, with no discernible safety differences. Bioavailability increased under fed conditions with the marketed tablet formulation.

Keywords

bioequivalence, food effect, Janus kinase inhibitor, peficitinib, pharmacokinetics

Rheumatoid arthritis (RA) is an inflammatory disease that is associated with chronic and painful joint inflammation. RA can cause cartilage and bone damage and, in some patients, progressive joint erosion, which is linked to physical disability and impaired quality of life.[1,2] The conventional synthetic disease-modifying antirheumatic drug (DMARD) methotrexate is approved as a first-line therapy for RA in Japan.[3] The issue of serious adverse events, such as pneumocystis pneumonia and lymphoproliferative diseases in Japan, however, means that the maximum dose of methotrexate is limited to 16 mg/week.[3] For those individuals who do not achieve a reasonable clinical response with methotrexate, options include the addition of a second conventional DMARD, the addition of a biological DMARD (such as a tumor necrosis factor inhibitor),

or the addition of a targeted synthetic DMARD (such as a Janus kinase [JAK] inhibitor).[3,4]

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Peficitinib (ASP015K) is an oral pan-JAK inhibitor that was approved in Japan in 2019 as a once-daily therapy for patients with RA. It is administered at a dose of 150 mg/day, with the option to reduce to 100 mg/day depending on the patient's condition. Peficitinib has demonstrated efficacy and safety at once-daily doses of up to 150 mg[5-7] in trials including patients with RA who had experienced an inadequate response to methotrexate[7] or conventional DMARDs.[6] Peficitinib administered at a dose of up to 150 mg was associated with significantly reduced RA symptoms versus placebo, as measured using the American College of Rheumatology 20 score.[5-7] Peficitinib was also associated with suppression of joint destruction, as measured with the van der Heijde-modified total Sharp score.[7] Overall, peficitinib was well tolerated; as with other JAK inhibitors,[8,9] reductions in neutrophil counts and increases in serious infections, such as herpes zoster, were observed compared with placebo.[5-7]

A mass balance clinical study showed that the metabolic clearance of peficitinib occurs mainly via 2 proposed pathways catalyzed by the sulfotransferase (SULT) isoenzyme, SULT2A1, and the methyltransferase isoenzyme, nicotinamide *N*-methyltransferase (NNMT),[10] of which genetic polymorphisms have not been reported so far. The pharmacokinetics (PK) of peficitinib have been further studied in healthy subjects[11] and in Japanese subjects with impaired renal or hepatic function.[12,13] In healthy subjects, the single-dose pharmacokinetics of peficitinib were characterized by dose proportionality for exposure (area under the plasma concentration-time curve [AUC_{inf}]) and maximum observed concentration (C_{max}) over a 3- to 300-mg dose range.[11] Across this dose range, peficitinib was absorbed rapidly, demonstrating time to C_{max} (T_{max}) of 1.0-1.8 hours and a mean terminal half-life ($t_{1/2}$) ranging from 2.8 to 12.9 hours. In addition, a 27% increase in exposure (AUC_{inf}) under fed conditions was observed.[11] The PK profile of a single oral dose of peficitinib (150 mg) was unaltered in subjects with renal or mild hepatic impairment, compared with subjects with normal renal or hepatic function.[12,13] However, exposure to peficitinib almost doubled in those with moderately impaired hepatic function.[13]

The PK profile of peficitinib has been further characterized in healthy subjects in the presence of the organic anion transporting polypeptide 1B1 substrate rosuvastatin and the P-glycoprotein (P-gp) inhibitor verapamil.[14,15] Although peficitinib in combination with rosuvastatin showed no clinically meaningful changes in exposure, coadministration with verapamil resulted in increased exposure of peficitinib and its metabolites, suggesting that P-gp is involved in the transport of peficitinib.[14,15]

In our bioequivalence study, the marketed tablet formulation of peficitinib was assessed for bioequivalence to the 150-mg tablet that was used in the phase 3 studies. Both these tablets were immediate-release formulations, but some of the excipients were different. In our food effect study, the effect of food on the PK and safety of a single oral dose of the marketed 150-mg peficitinib tablet formulation were examined.

Methods

Study Design and Participants

Study Conduct and Ethical Considerations. The bioequivalence study (NCT02531191) and the food effect study were both conducted at the Sumida Hospital, Tokyo, Japan, during June–July 2015 and November 2015–February 2016, respectively. The studies were conducted in accordance with the respective study protocols, Good Clinical Practice guidelines, the International Council on Harmonization guidelines, applicable regulations and guidelines governing conduct of clinical and bioequivalence studies, and the ethical principles that have their origin in the Declaration of Helsinki. The local institutional review board (Hakata Clinic Institutional Review Board, Fukuoka, Japan) reviewed and approved the study protocols and the informed consent documents. Each participant provided written informed consent before treatment initiation.

Study Design. Both studies were Japanese open-label, randomized, single-dose, 2-way crossover studies, with each period of the crossover conducted over 4 days. The plan for the bioequivalence study (NCT02531191) was that 40 healthy volunteers would receive a single oral dose of peficitinib 150 mg. Half the subjects were randomized to receive the marketed tablet followed by the tablet used in the phase 3 studies in the 2 crossover periods (n = 20), whereas the remaining subjects received the tablet used in the phase 3 studies followed by the marketed tablet during the crossover periods (n = 20). The tablets were administered with 200 mL of water following an overnight fast of at least 10 hours in each period. Food was not allowed for 4 hours after dosing. Apart from the water provided for tablet administration, no further water was allowed during the hour before and the hour after dosing.

In the food effect study, 18 healthy volunteers were scheduled to receive a single oral dose of the marketed 150-mg peficitinib tablet under fed or fasted conditions on day 1 of each study period. Nine participants received peficitinib under fasted conditions in period 1 and under fed conditions in period 2; the other 9 participants received peficitinib under fed conditions in period 1 and under fasted conditions in period 2. For administration under fasted conditions, food intake was not permitted overnight for at least 10 hours before

dose, and the study drug was received on day 1 with 200 mL of water and no breakfast. For administration underfed conditions, food was not permitted for at least 10 hours overnight, and the study drug was received on day 1 with 200 mL of water and a high-fat breakfast of ≥ 900 kcal and $\geq 35\%$ lipid content.[16] Participants were advised to consume the meal within 20 minutes, and the study drug was administered within 10 minutes of finishing breakfast. No water was allowed within the period 1 hour before dose and 1 hour after dose, except for study drug administration and breakfast.

Inclusion and Exclusion Criteria. Both studies included healthy men aged 20 to <45 years, with a body weight of 50 to <80 kg and a body mass index of 17.6 to <26.4 kg/m^2 who were using 2 forms of contraception, including 1 barrier method. Subjects were excluded if they had a history of upper gastrointestinal symptoms in the 7 days preceding the study or had a history of serious or disseminated herpes zoster, more than 1 relapse of localized herpes zoster, or hospitalization because of serious infection within 90 days before day −1 of the first study period.

Sample Collection

Samples for PK analysis were collected before dosing, then 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60 (food effect study only), and 72 hours after dose. Approximately 2 mL of blood was taken by venipuncture or cannulation of a forearm vein and collected into vacutainer tubes containing tripotassium hydrogen ethylenediaminetetraacetate.

Pharmacokinetic Assessments

The concentration of plasma peficitinib was measured using a validated liquid chromatography-tandem mass spectrometry method at LSI Medience Corporation (Itabashi-ku, Tokyo, Japan). The lower limit of quantification was 0.2500 ng/mL when 25 μL of plasma was used. Values below the limit of quantification were entered as 0. The analysis method has been previously published using rat plasma.[17] The primary analysis to determine bioequivalence was based on PK parameters: AUC from zero to the final sample (AUC_t) and C_{max}. Secondary end points were based on analyses performed on AUC_{last} and AUC_{inf}. In the food effect study, AUC_{inf}, AUC_{last}, apparent total systemic clearance, C_{max}, $t_{\frac{1}{2}}$, and T_{max} were calculated. Analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina) and Phoenix WinNonlin version 6.2 (Certara USA, Inc., Princeton, New Jersey) software. AUC_{inf}, AUC_{last}, and AUC_t in the bioequivalence study were calculated by the linear trapezoidal rule (Linear Trapezoidal Linear Interpolation option)

in Phoenix WinNonlin; AUC_{inf} and AUC_{last} in the food effect study were calculated with the Linear Up/Log Down option in Phoenix WinNonlin.

Safety

Safety was assessed by evaluation of adverse events, vital signs, and laboratory variables. Adverse events were defined as any untoward medical occurrences and were monitored continually during the study period. Vital signs were monitored before dosing, 2 hours after dosing, and on days 2, 3, and 4 of the study. Participants had a 12-lead electrocardiogram (ECG) before dosing, 2 hours after dosing, and at the end of the study. Laboratory variables (hematology, urinalysis, and blood chemistry) were measured before dosing and at the end of the study.

Statistical Analysis

For the bioequivalence study, a total of 40 subjects were required to be enrolled for the 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) to fall between 0.8 and 1.25 with 80% power. The sample size was estimated using an SAS POWER procedure with the following conditions: alpha = 5%, power = 80%, GMR = 1.05 for PK parameters and coefficient of variation (CV %) for C_{max} = 33.7% and AUC = 25.3%, from a previous bioavailability study[18]; lower and upper bounds for PK parameters were 0.80 and 1.25, respectively, in a 2×2 crossover study. All participants who received at least 1 dose of study drug were included in the safety analysis set (SAF). Subjects who received study drug and provided at least 1 sample for the measurement of drug concentrations were included in the PK analysis set (PKAS); from the PKAS, subjects who provided complete sets of PK samples with concentration measurements in the 2 periods were included in the bioequivalence analysis set (BEAS). For the primary analysis, log-transformed C_{max} and AUC_t were employed for the analysis of variance (ANOVA) using the SAS MIXED procedure, with treatment, group, and dosing period as fixed effects and subjects as a random effect. Bioequivalence between the marketed tablet and the tablet used in the phase 3 studies was declared when the 90%CIs of the GMRs for C_{max} and AUC_t were within the range of 0.8–1.25.[16]

For the food effect study, 18 subjects (9 per sequence) were considered sufficient to investigate the effect of food on the PK of the marketed 150-mg peficitinib tablet formulation; no statistical power calculation was used to determine the sample size. All participants who received at least 1 dose of the study drug were included in the SAF. All subjects who received the study drug and had at least 1 PK parameter available were included in the PKAS, which was used for the

Table 1. Baseline Demographic Characteristics of Subjects in the Bioequivalence and Food Effect Studies (SAF)

Parameter, Mean $\pm$ SD	Bioequivalence Study (n = 40)	Food Effect Study (n = 18)
Age, years	30.5 $\pm$ 7.5	30.2 $\pm$ 7.6
Weight, kg	63.8 $\pm$ 7.2	64.3 $\pm$ 7.1
BMI, kg/m^2	21.5 $\pm$ 2.4	21.5 $\pm$ 1.8

BMI, body mass index; SAF, safety analysis set—all participants who received at least 1 dose of the study drug; SD, standard deviation.

All participants who received at least 1 dose of the study drug were included in the SAF. In the food effect study, 1 randomized participant was discontinued from the study because of thrombotic cerebral infarction during the washout period (after study drug administration under fasted conditions).

food effect assessment. The food effect was evaluated using the log-transformed AUC_{last}, AUC_{inf}, and C_{max} for the ANOVA by the SAS MIXED procedure, with treatment, group, and dosing period as fixed effects and subjects as a random effect.

Results

Disposition and Demographics of Subjects

Bioequivalence Study.   In total, 40 healthy male subjects were randomized into 1 of the 2 treatment sequences (Table 1). Thirty-nine subjects completed the study, and 1 discontinued because of an adverse event (upper respiratory tract infection) not related to the study drug. All 40 subjects were included in the SAF and PKAS; 39 were included in the BEAS—the subject who discontinued had an incomplete set of PK samples and was excluded.

Food Effect Study.   A total of 18 subjects were randomized to receive treatment and were included in the SAF and PKAS (Table 1). One subject was discontinued from the study because of an adverse event (thrombotic cerebral infarction); all other subjects completed the study.

Pharmacokinetics

Bioequivalence Study.   Pharmacokinetic profiles in the bioequivalence study were similar for both the marketed tablet and the tablet used in the phase 3 studies (Figure 1a). The mean plasma PK parameters of peficitinib in the bioequivalence study are shown in Table 2a. The 90%CIs of the GMRs for C_{max} and AUC_t of peficitinib were within the predefined limits of 0.8 to 1.25, confirming the bioequivalence of the marketed tablet and the tablet used in the phase 3 studies, under fasted conditions (Table 3). In a secondary statistical analysis, the 90%CIs of GMRs for AUC_{last} and AUC_{inf} were also within the predefined limits of 0.8 to 1.25.

Food Effect Study.   The PK of peficitinib, administered as a single oral dose of 150 mg under fed con-

ditions compared with fasted conditions, was assessed using the primary PK parameters AUC_{last} and C_{max}, as shown in Figure 1b and Table 4. Under fed conditions, the AUC_{last} was 36.8% higher, and the C_{max} was 56.4% higher than under fasted conditions (Table 4). Table 2b shows the mean plasma PK parameters of peficitinib in the food effect study.

Safety

A single 150-mg peficitinib oral dose of the marketed tablet or the tablet used in the phase 3 studies was well tolerated by healthy male subjects in the bioequivalence study, and the marketed 150-mg peficitinib tablet was well tolerated under both fed and fasted conditions in the food effect study. No deaths were reported in either study.

Bioequivalence Study.   In total, 3 adverse events were reported in 3 of the 40 subjects during the study (7.5%), 2 after receiving the marketed tablet (diarrhea and upper respiratory tract infection [URTI]) and 1 (headache, which resolved by study end) after receiving the tablet used in the phase 3 studies. The diarrhea and headache events were considered treatment related. The diarrhea resolved by the end of treatment, but the URTI was unresolved at the time of study discontinuation. All adverse events were considered mild or moderate in severity. No serious adverse events were reported. One subject experienced a URTI leading to discontinuation after receiving the marketed tablet, but this was moderate in intensity and not considered related to the study drug. There were no clinically relevant changes in laboratory results, vital sign measurements, or 12-lead ECG results.

Food Effect Study.   Two participants in each of the fed and fasted states experienced treatment-emergent adverse events, of which 3 were deemed to be related to the study drug (moderate headache under fed conditions [n = 1] and mild headaches under fed and fasted conditions [n = 2]). All headaches resolved. One individual experienced a serious adverse event (moderate thrombotic cerebral infarction) after dosing during fasted conditions, which was not considered related to the study drug. This subject was discontinued from the study, and the event resolved during the follow-up period. No trends associated with fed or fasted conditions were observed in adverse events, laboratory results, vital sign measurements, or 12-lead ECG results.

Discussion

These open-label, single-dose, 2-period, 2-sequence, randomized crossover studies of peficitinib demonstrated bioequivalence between 2 different 150-mg tablet formulations and the increased bioavailability of peficitinib after food. First, we conducted a
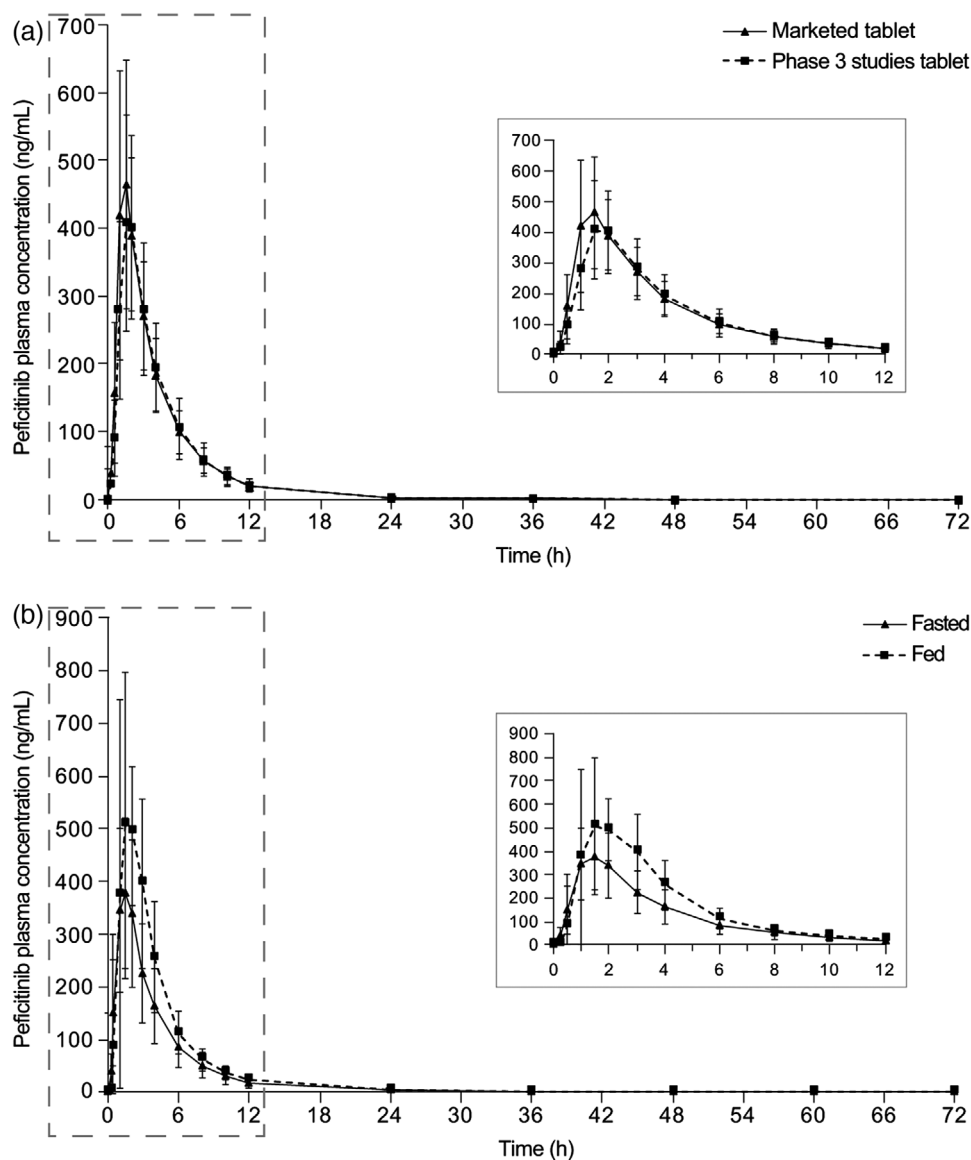
Figure 1. Plasma peficitinib concentrations after (a) a single 150-mg dose of either the marketed or the phase 3 studies tablet formulation (BEAS) or (b) a single 150-mg dose of the marketed tablet formulation in a fed or fasted state (PKAS). BEAS, bioequivalence analysis set—all participants who provided complete sets of pharmacokinetic samples with concentration measurements in both the 2 periods in accordance with the study protocol; PKAS, pharmacokinetic analysis set—all participants who received the study drug and had at least 1 pharmacokinetic parameter available. Data are arithmetic means ± standard deviation.

bioequivalence study under fasted conditions, which is considered more sensitive than the fed condition to detect a potential difference between formulations.[19] Bioequivalence between the 2 formulations was demonstrated with AUC_t, AUC_{inf}, and AUC_{last} (Table 3), in line with Japanese, FDA, and EMA guidelines.[16,20,21] Second, our food effect study demonstrated that the bioavailability of peficitinib, as assessed using both AUC_{last} and C_{max}, was increased under fed versus fasted conditions. Findings from our study, conducted using the currently marketed tablet formulation, are similar to those of the previous phase 1 study, which

used a different capsule formulation and also showed an increase in peficitinib exposure following a meal.[11] The efficacy and safety of peficitinib were demonstrated in phase 2b and 3 studies in which peficitinib was administered after a meal. Therefore, the results from both PK studies presented here, along with the data from the phase 2b and 3 trials, indicate that peficitinib tablets should be taken after food.

Peficitinib is a weak-base drug and has a low aqueous solubility of ≤ 0.1 mg/mL at pH 7.[18] Drugs with low solubility and high permeability (Biopharmaceutics Classification System [BCS] class II) generally show a

Table 2. Mean Plasma Pharmacokinetic Parameters for Peficitinib in (a) the Bioequivalence Study (BEAS) and (b) the Food Effect Study (PKAS)

(a)

Parameter, Mean $\pm$ SD	Marketed Tablet (n = 39)	Phase 3 Studies Tablet (n = 39)
AUC_{last} (ng·h/mL)	1918 $\pm$ 410.6	1838 $\pm$ 451.3
AUC_{inf} (ng·h/mL)[a]	1932 $\pm$ 417.5	1832 $\pm$ 440.9
AUC_t (ng·h/mL)	1924 $\pm$ 410.3	1843 $\pm$ 450.6
C_{max} (ng/mL)	524.5 $\pm$ 183.8	466.6 $\pm$ 139.7
CL/F (L/h)[a]	85.7 $\pm$ 46.2	88.7 $\pm$ 33.4
T_{max} (h)	1.5 $\pm$ 0.6	1.8 $\pm$ 0.8
$t_{\frac{1}{2}}$ (h)[a]	9.4 $\pm$ 7.4	10.6 $\pm$ 9.8

(b)

Parameter, Mean $\pm$ SD	Fasted Condition (n = 18[b])	Fed Condition (n = 17[b])
AUC_{last} (ng·h/mL)	1645 $\pm$ 506.5	2217 $\pm$ 441.9
AUC_{inf} (ng·h/mL)	1665 $\pm$ 518.3	2227 $\pm$ 440.5
C_{max} (ng/mL)	447.6 $\pm$ 138.7	698.5 $\pm$ 213.2
CL/F (L/h)	98.4 $\pm$ 29.5	70.2 $\pm$ 15.9
T_{max} (h)	1.6 $\pm$ 0.5	2.0 $\pm$ 0.8
$t_{\frac{1}{2}}$ (h)	12.0 $\pm$ 11.3	9.3 $\pm$ 7.8

AUC_{last}, area under the concentration-time curve from the time of dosing to the last measurable concentration; AUC_{inf}, AUC from the time of dosing extrapolated to infinity; AUC_t, AUC from zero to the final sampling time; BEAS, bioequivalence analysis set—all participants who provided complete sets of pharmacokinetic samples with concentration measurements in the 2 periods in accordance with the study protocol; CL/F, apparent total systemic clearance; C_{max}, maximum plasma concentration; SD, standard deviation; PKAS, pharmacokinetic analysis set—all participants who received the study drug and had at least 1 pharmacokinetic parameter available; T_{max}, time to maximum plasma concentration; $t_{\frac{1}{2}}$, half-life.
[a] n = 37 and n = 38 in the marketed and phase 3 studies tablet formulation groups, respectively.
[b] In the food effect study, 1 randomized participant was discontinued from the study because of a thrombotic cerebral infarction during the washout period (after study drug administration under fasted conditions).

Table 3. Ratios of Geometric Means for Pharmacokinetic Parameters in the Bioequivalence Study (BEAS)

Parameter	GMR (90%CI of GMR[a])
C_{max} (ng/mL)	1.109 (0.991–1.241)
AUC_t (ng·h/mL)	1.046 (0.946–1.156)
AUC_{inf} (ng·h/mL)	1.046 (0.949–1.154)
AUC_{last} (ng·h/mL)	1.046 (0.944–1.159)

AUC_{last}, area under the concentration–time curve from the time of dosing to the last measurable concentration; AUC_{inf}, AUC from the time of dosing extrapolated to infinity; AUC_t, AUC from 0 to the final sampling time; BEAS, bioequivalence analysis set—all participants who provided complete sets of pharmacokinetic samples with concentration measurements in the 2 periods in accordance with the study protocol; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric least-squares mean ratio.
Ratios are presented for the marketed tablet versus the phase 3 studies tablet for each pharmacokinetic parameter.
[a] The difference of least-squares means of log-transformed pharmacokinetic parameters between the marketed tablet formulation and the phase 3 studies tablet and its 90%CI are back-transformed to the raw scale and expressed as percent.

Table 4. Comparison of the Pharmacokinetics of a Single Oral Dose of Peficitinib Under Fed and Fasted Conditions in the Food Effect Study (PKAS)

Parameter	GMR (90%CI of GMR[a])
AUC_{last}	1.368 (1.227–1.525)
AUC_{inf}	1.358 (1.221–1.510)
C_{max}	1.564 (1.388–1.762)

AUC_{last}, area under the concentration–time curve from the time of dosing to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric least-squares mean ratio; PKAS, pharmacokinetic analysis set—all participants who received the study drug and had at least 1 pharmacokinetic parameter available.
[a] The difference of least-squares means of log-transformed pharmacokinetic parameters between the fasted condition and the fed condition and its 90%CI are back-transformed to the raw scale and expressed as ratios. Ratios are presented for the fed condition versus the fasted condition for both parameters.

positive food effect, whereas the effect of food on drugs with low solubility and low permeability (BCS class IV drugs) is more complex.[22] Although it can be difficult to anticipate the impact of food on a BCS class IV drug, a study comparing BCS class with an observed human food effect found that a large majority of the class IV compounds included in the analysis showed a positive food effect.[23] The results of a mass balance study

suggested that peficitinib was not highly permeable[10] and that it would therefore be considered a BCS class IV drug. It is likely that the increased bile concentration in the small intestine in the fed state enhances the solubility of peficitinib, resulting in the positive food effect in humans.

A single oral dose of 150 mg peficitinib was well tolerated for both the marketed tablet and the tablet used in the phase 3 studies and under fed or fasted conditions. The treatment-emergent adverse event of diarrhea reported in the bioequivalence study was previously reported in the phase 2b study, and the headaches reported in the bioequivalence and food effect studies were previously observed in both the phase 2b and 3 studies, but were not included in the safety discussions of the publications.[5-7] Overall, these PK studies are generally consistent with the safety and tolerability profile of peficitinib that was demonstrated in the phase 2b and 3 studies.[5-7]

The PK studies reported here were performed with the maximum 150-mg dose of peficitinib, as the studies were conducted before the reporting of phase 3 study data and, therefore, before a decision regarding which dose would be licensed for treatment of RA. The 50- and 100-mg tablets that were subsequently licensed for treatment of RA are bioequivalent to the marketed 150-mg tablets according to in vitro studies.[18]

There are possible limitations to these studies that may restrict the generalizability of the data, including its relevance for a non-Japanese/non-Asian population. Although no genetic polymorphisms have been reported for the metabolic enzymes of peficitinib (SULT2A1 and NNMT), interethnic differences in the PK of peficitinib have been observed; in particular, peficitinib exposure appears higher in East Asian compared with non-East Asian subjects,[15] but the reason for this difference remains unknown. Both studies enrolled only male participants; however, there were no differences in the PK of peficitinib between males and females in a previous study,[11] so we consider this unlikely to affect the interpretation of the data in relation to a mixed-sex population. Both studies also enrolled only healthy subjects, which may affect the generalizability of the results to individuals with RA. To address these potential intrasubject variabilities, the bioequivalence and food effect studies included a crossover design to enable the results to be extrapolated to patients with RA, regardless of race or sex.

Conclusions

The marketed 150-mg tablet formulation of peficitinib was bioequivalent to the 150-mg tablet formulation used in the phase 3 studies with no discernible differences in safety outcomes. The bioavailability of pefici-

tinib increased under fed conditions with the marketed tablet formulation. Peficitinib was well tolerated by healthy Japanese male subjects under fed and fasted conditions when a single oral dose of the marketed 150-mg tablet was administered.

Author Contributions

All authors met the following criteria for authorship: substantial contributions to the acquisition, analysis, and interpretation of data for the work; contribution to drafting the work and revising it critically; providing final approval of the version submitted; and agreeing to be accountable for all aspects of the work.

Compliance With Ethics Guidelines

Institutional review board-approved written informed consent was obtained from each subject before the initiation of any study-specific procedures. This study was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice, International Conference on Harmonization guidelines, and applicable laws and regulations.

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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