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Effects of Meal Type on the Oral Bioavailability of the ALK Inhibitor Ceritinib in Healthy Adult Subjects

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Abstract

Ceritinib is a potent inhibitor of anaplastic lymphoma kinase (ALK), which has shown acceptable safety and substantial antitumor activity in ALK-positive non–small cell lung cancer (NSCLC) patients. Two food-effect studies were conducted in healthy adults to investigate the influence of food on the oral bioavailability of ceritinib: a study with low- or high-fat meals at 500 mg and a study with a light snack at 750 mg. Compared with the fasted state, $AUC_{0-\infty}$ (90%CI) of ceritinib was increased by 58% (34%, 86%) after the intake of a low-fat meal, by 73% (46%, 105%) after the intake of a high-fat meal, and by 54% (19%, 99%) after the intake of a light snack. Safety assessments also suggested that food may improve gastrointestinal (GI) tolerability after a single ceritinib dose. Based on the pharmacokinetic results, it is essential to avoid any type of meal during dosing of ceritinib because the intake of food may increase the occurrence of exposure-dependent, non-GI toxicities at the labeled dose of 750 mg daily during fasting. A randomized trial is ongoing to determine an alternative way to give ceritinib (450 mg or 600 mg with food) that may enhance GI tolerability in ALK-positive NSCLC patients.

Keywords

ceritinib, anaplastic lymphoma kinase, healthy subjects, pharmacokinetics, food effect

In anaplastic lymphoma kinase (ALK)-positive non–small cell lung cancer (NSCLC), ALK rearrangements serve as a key oncogenic driver. Therefore, a rational therapeutic approach to improve outcomes for these patients is ALK-targeted inhibition.[1,2] The first evidence of ALK-positive NSCLC's response to ALK inhibitors was demonstrated with crizotinib,[3] a first-in-class orally bioavailable adenosine triphosphate-competitive inhibitor of ALK. Crizotinib is approved for the treatment of ALK-positive NSCLC and has been shown to be superior to chemotherapy in 2 randomized single-agent trials.[4,5] Although crizotinib is effective in patients with ALK-positive NSCLC, disease progression invariably occurs, typically within 1 year of starting treatment, due to the development of acquired drug resistance.[6,7] Therefore, the development of more selective and potent ALK inhibitors is crucial for patients whose tumors have progressed after crizotinib or who are intolerant to crizotinib.

Ceritinib (LDK378, Zykadia™; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey) is a novel and highly selective inhibitor of ALK. In comparison with crizotinib, ceritinib is approximately 20-fold more potent at inhibiting ALK in vitro and also maintains activity against several mutated versions of ALK that confer resistance to crizotinib.[8] In a phase 1 dose-escalation and expansion study with ceritinib, oral dose levels ranging from 50 to 750 mg daily administered under fasting conditions (no food consumed at least 2 hours before and 2 hours after dosing) in patients with ALK-positive advanced tumors, 750 mg ceritinib daily showed a manageable safety profile and produced substantial antitumor activity in NSCLC.[9] Based on these study results, ceritinib was granted accelerated approval in the United States[10] and conditional approval in the European Union for the treatment of patients with ALK-positive NSCLC previously treated with crizotinib.[11]

Ceritinib has a molecular weight of 558.14 Da and two pKa values, 4.1 and 9.7.[10] The drug is formulated as a hard gelatin capsule for oral administration. Ceritinib shows good solubility (11 mg/mL) at pH 1 and poor solubility (<0.01 mg/mL) at pH 6.8. Its gastrointestinal (GI) permeability is determined to be low based on low in vitro passive permeability and efflux transport mediated by P-glycoprotein (P-gp) across the Caco-2 cell monolayer.[10–12] Because the physicochemical characteristics of a drug may also impact its biopharmaceutic and pharmacokinetic (PK) properties, it was of interest to

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assess the effect of food intake on the oral bioavailability of ceritinib in human subjects, as the presence of food may enhance absorption, resulting in increased ceritinib exposure in vivo, which in turn could lead to changes in drug efficacy and toxicity. In addition, it has been previously reported that food intake may improve the GI tolerability of orally administered tyrosine kinase inhibitors (TKIs).[13,14]

We report here, in detail, the results from the 2 open-label, randomized, 2-period crossover food-effect studies, which examined the influence of meals with various fat content (low-fat meal, high-fat meal, and light snack), on the bioavailability of ceritinib as well as on its GI tolerability in healthy subjects.

Materials and Methods

Both food-effect studies were conducted at PPD Development LLC (Austin, Texas); the study protocol and informed consent forms were approved by an Institutional Review Board. All subjects provided written informed consent prior to their participation in the study.

Eligibility

Participants consisted of healthy adults aged 18 to 55 years with a body weight $\geq$50 kg and a body mass index of 18 to 30 kg/m^2. Women were postmenopausal or surgically sterilized. Subjects were excluded if they had used any prescription drug or medications that are cytochrome P450 3A (CYP3A) inhibitors or inducers within 30 days of study initiation or had used any over-the-counter medications, herbal supplements, or vitamins within 4 weeks of study initiation. Consumption of grapefruit, star fruit, pomegranate, and cruciferous vegetables within 7 days prior to study initiation was prohibited. Subjects were also excluded if they had used alcohol and/or drugs within 3 days of study initiation. Consumption of xanthine-containing (eg, caffeine) food or beverages within 48 hours of study initiation was prohibited.

Study Design

The first food-effect study was a randomized, open-label study to assess the effect of a low- or high-fat meal on the bioavailability of a single 500 mg dose of ceritinib in healthy subjects. This study tested a low-fat meal against fasting conditions and a high-fat meal against fasting conditions separately, with each comparison in a 2-treatment, 2-period crossover design. Twenty-eight subjects were randomized (with 14 for each comparison) into 1 of 4 treatment sequences and underwent 2 treatment periods, period 1 (days 1-13) and period 2 (days 14-22). The 2 treatment periods were separated by a 2-week washout. All subjects were confined at the study center during the drug administration and the PK assessment periods. The study completion evaluation was conducted on day 22, 8 days after the last dose of the study drug had been given. During each study period, after an overnight fast of approximately 10 hours, subjects received a single 500 mg oral dose of ceritinib following either the fasting or fed condition: (A) under fasting conditions, (B) 30 minutes after a low-fat breakfast, or (C) 30 minutes after a high-fat breakfast. All subjects remained fasted for at least 4 hours after dosing on day 1 and day 15. The treatment sequences were A-B and B-A for the low-fat cohort and A-C and C-A for the high-fat cohort. The high-fat breakfast contained approximately 1000 total calories and 58 g of fat with a composition of 50% fat, 35% carbohydrates, and 15% protein as recommended in the Food Effect FDA Guidance for Industry.[15] It comprised 2 fried eggs, 2 slices of toast with butter, 3 strips of bacon, 1 teaspoon of jelly, 4 oz of hash brown potatoes, and 8 oz of whole milk. The low-fat breakfast contained approximately 330 calories and 9 g of fat with a composition of 25% fat, 60% carbohydrates, and 15% protein. It comprised 2 slices of toast with 1 teaspoon of low-fat margarine, 1 teaspoon of jelly, and 8 oz of skimmed milk.

The second food-effect study employed a randomized, open-label, 2-period crossover design to assess the effect of a light snack on the bioavailability of a single 750 mg ceritinib dose in healthy subjects. Twelve subjects were randomized into 1 of the 2 treatment sequences and underwent 2 treatment periods, period 1 (days 1-15) and period 2 (days 16-24). The 2 treatment periods were separated by a 16-day washout. All subjects were confined at the study center during the drug administration and PK assessment periods. The study completion evaluation was conducted on day 24, 8 days after the last dose of the study drug had been given. During each study period, after an overnight fast of approximately 10 hours, subjects received a single 750 mg oral dose of ceritinib following 1 of the 2 treatments: (A) under fasting conditions, or (B) 30 minutes after a light snack. All subjects remained fasted for at least 4 hours after dosing on day 1 and day 17. The light snack contained approximately 100 to 300 calories and 1.5 g of fat. It comprised a 3.63-oz pudding cup (Jell-O^{TM}) or 1 slice of toast with 1 teaspoon of jelly and 8 oz of skimmed milk.

For both studies, serial blood samples for ceritinib concentration determination were collected after each ceritinib administration at predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose. At each time point, 2.0 mL of whole blood was drawn using a tube containing ethylenediaminetetraacetic acid. Each sample was gently inverted several times to ensure adequate mixing of the contents. The tube was allowed to stand vertically in an ice bath for 30 minutes prior to centrifugation at 3−5°C for 15 minutes at 1100 g. Immediately after centrifugation, the upper plasma sample

was transferred and stored frozen below −70°C until shipped to the analytical site for sample analyses.

Assessments

Determination of Plasma Concentrations of Ceritinib. Plasma concentrations of ceritinib were measured using a validated liquid chromatography/tandem mass spectrometry assay described previously.[16] The lower limit of quantification for ceritinib was estimated at 1.00 ng/mL using a 100-μL plasma sample.

Pharmacokinetic Analysis. The following PK parameters of ceritinib were calculated using the standard noncompartmental method with Phoenix WinNonlin (version 6.2; Pharsight, Mountain View, California): area under the curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), apparent oral clearance (CL/F), and apparent volume of distribution at the terminal phase of elimination (V_z/F). Actual sampling times were used for PK calculations in all studies.

AUC values were calculated using the linear trapezoidal rule. None of the $AUC_{0-\infty}$ values had more than 15% extrapolation. The $t_{1/2}$ was calculated as $\ln 2/\lambda_z$, where λ_z was estimated by linear regression of the terminal log-linear portion of the concentration-time curve. The CL/F and V_z/F were calculated as the ratio of dose to $AUC_{0-\infty}$ and ratio of CL/F to λ_z, respectively.

Safety and Tolerability Assessments. General safety parameters of the healthy subject studies were evaluated including adverse events (AEs), vital signs, physical examination, clinical laboratory testing (including hematology, blood chemistry including liver function, and urinalysis), and electrocardiograms. AEs were graded according to the Common Terminology Criteria for AEs, version 4.03. A subject with multiple occurrences of an AE (regardless of study drug relationship) was counted only once in the AE category regardless of which treatment period the event occurred. Furthermore, to evaluate the influence of dose and prandial condition on the frequency of GI AEs, selected GI AEs, such as diarrhea, nausea, and vomiting, were also summarized across the 2 healthy subject studies when subjects received ceritinib alone under fasting or fed conditions; ie, a summary of these GI AEs was by treatment period (fasting or fed) such that multiple AEs, if they occurred in the same treatment period, were only counted once in the AE category for that period.

Statistical Analysis

The PK parameters of ceritinib were summarized by descriptive statistics, including geometric mean and coefficient of variation. Median values and ranges were provided for t_{max}.

On the basis of previous studies, it was estimated that a sample size of 28 subjects (7 per sequence) for the food-effect study with low- or high-fat meals, and 12 (6 per sequence) for the food-effect study with a light snack would provide adequate precision of the estimated difference between treatments in terms of 90% confidence intervals (CIs) of the geometric mean ratio of AUC and C_{max}. These calculations were based on estimates of intrasubject variability of AUC and C_{max} of ceritinib obtained from previous studies. The sample size of 28 and 12 also took into account a possible dropout rate of 10%.

For the assessment of the food effect on ceritinib PK, a linear mixed-effects model was fitted to the log-transformed PK parameters $AUC_{0-\infty}$, and C_{max} using SAS PROC MIXED (SAS Institute Inc., Cary, North Carolina). The model included sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect. The food intake-related effect was evaluated using the estimated geometric mean ratios of $AUC_{0-\infty}$ and C_{max} for ceritinib treatment between fed and fasting conditions and their corresponding 90% CIs. If the 90%CIs of the geometric mean ratio for C_{max} and $AUC_{0-\infty}$ and were completely contained within the range of 0.8 to 1.25 for test (fed conditions) vs reference (fasting conditions), then bioequivalence was concluded.[15]

The number and percentage of subjects with any AE, as well as selected GI AEs (diarrhea, nausea, and vomiting), were summarized by dose and prandial condition (fasting vs fed) in healthy subjects.

Results

Food-Effect Study With Low- and High-Fat Meals in Healthy Subjects

A total of 28 subjects (21 males, 7 females) were enrolled, and 27 subjects completed the study per protocol. One subject discontinued from the study due to grade 3 blood creatine phosphokinase (CPK) increase. The median age of the subjects enrolled in this study was 36 years (range: 21 to 55 years). The majority of subjects were male (75%) and white (68%).

Following a single oral administration of 500 mg ceritinib under fasting or fed conditions, ceritinib experienced a prolonged absorption phase with median t_{max} occurring at 7 to 10 hours (Table 1). Median t_{max} in healthy subjects was slightly greater than that observed in patients,[12] possibly due to the slightly different PK sampling schemes used in the 2 studies. No apparent differences in C_{max} and AUC of ceritinib were observed between healthy subjects under fasting conditions and patients at the same dose level.[12] Relative to administration under fasting conditions, the median t_{max} of ceritinib was not markedly altered when the drug was administered with a low-fat meal but was slightly delayed by 2 hours after a high-fat meal. As shown in Figure 1, the mean

Table 1. Summary of Ceritinib Pharmacokinetic Parameters Under Fasting or Fed Conditions in Food-Effect Studies Conducted in Healthy Subjects

Treatment	n	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (hours)	$t_{1/2}$ (hours)	CL/F (L/h)	V_z/F (L)
Food effect of low- and high-fat meals (500 mg of ceritinib)							
F	27	6910 (41.8)	159 (43.5)	8.00 (6.00-12.0)	36.2 (23.9)	72.3 (41.8)	3770 (55.1)
LF	14	10 300 (22.6)	220 (19.7)	7.00 (3.00-12.1)	34.6 (11.9)	48.4 (22.6)	2410 (28.0)
HF	14	12 700 (31.7)	235 (29.4)	10.0 (6.00-12.0)	34.2 (15.2)	39.3 (31.7)	1940 (35.2)
Food effect of light snack (750 mg of ceritinib)							
F	12	9390 (82.2)	213 (71.7)	6.02 (6.00-10.0)	35.6 (13.0)	79.9 (82.2)	4100 (74.7)
LS	12	14 500 (41.7)	308 (39.9)	8.02 (6.00-10.1)	40.2 (25.2)	51.8 (41.7)	3010 (51.8)

$AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; CL/F, apparent oral clearance; C_{max}, maximum plasma concentration; F, fasting conditions; HF, high-fat meal; LF, low-fat meal; LS, light snack; n, number of evaluable subjects; $t_{1/2}$, terminal elimination half-life;t_{max}, time to peak plasma concentration; V_z/F, apparent volume of distribution.

Values presented are median (range) for t_{max}, geometric mean (CV% of geometric mean) for all others.

concentration-time profiles revealed higher plasma concentrations for ceritinib when it was administered under fed conditions (low- and high-fat meals). Relative to the fasting conditions, the C_{max} and $AUC_{0-\infty}$ were increased by 43% and 58%, respectively, after the intake of a low-fat meal, and by 41% and 73%, respectively, after the intake of a high-fat meal (Table 2). The intersubject variability of PK parameters, as estimated by geometric mean CV%, under fed conditions was generally lower than that under fasting conditions (Table 1).

Food-Effect Study With a Light Snack in Healthy Subjects

A total of 12 subjects (10 males, 2 females) were enrolled, and 11 subjects completed the study per protocol. One subject withdrew consent from study participation prematurely on day 21 (96 hours postdose during period 2) due to a family emergency. The median age of the subjects enrolled in this study was 40 years (range 22 to 55 years). The majority of subjects were male (90%) and white (53%).

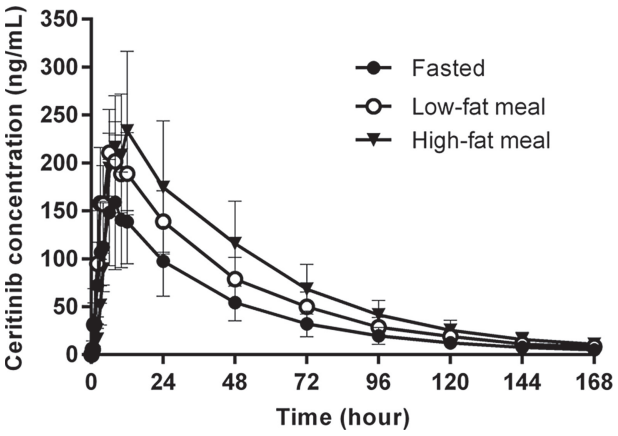

Figure 1. Linear plot of plasma ceritinib after a single oral 500 mg dose under fasting conditions or with a low- or high-fat meal. Data are presented as arithmetic mean (± SD).

Following a single oral administration of 750 mg ceritinib, fasted or with a light snack, the median t_{max} was attained at 6 to 8 hours (Table 1). As shown in Figure 2, the mean plasma concentrations of ceritinib were generally higher after the administration of ceritinib with a light snack. Relative to the fasting conditions, the C_{max} and $AUC_{0-\infty}$ of ceritinib were increased by 45% and 54% (Table 2), respectively, which is consistent with the results when a single oral dose of ceritinib was administered with a low-fat meal as described above. The intersubject variability of AUC and C_{max}, as estimated by geometric mean CV%, decreased approximately 50% when ceritinib was administered with a light snack as compared to the fasted state.

Safety and Tolerability

Ceritinib administered over the 500 to 750 mg single dose range was well tolerated in healthy subjects. Most AEs were mild (grade 1; 21 out of 40 subjects [52.5%]) or moderate (grade 2; 1 out of 40 subjects [2.5%]) in severity and resolved within a week. In both studies no deaths, serious AEs, or other significant AEs were reported. In addition, none of the subjects had clinically significant changes in vital signs or clinically significant ECG changes.

Two subjects experienced grade 3 AEs. In the food-effect study with low- and high-fat meals, 1 subject experienced grade 3 blood CPK increase, which was attributed, by the investigator, to vigorous physical activity during the washout period of the study. The subject discontinued from the study due to this AE, although CPK elevation was considered not to be related to ceritinib. In the food-effect study with a light snack, 1 subject experienced grade 3 diarrhea, which resolved on the same day of onset without the use of any concomitant medication.

The most common category of AEs was GI disorders, which is consistent with the safety profile reported in the phase 1 patient trial after either a single dose (data on file,

Table 2. Geometric Mean Ratio for Ceritinib Primary Pharmacokinetic Parameters Under Fasting or Fed Conditions in Food-Effect Studies Conducted in Healthy Subjects

Pharmacokinetic Parameter	Treatment	n	Adjusted Geometric Mean	Comparison	Geometric Mean Ratio (90%CI)
Food effect of low- and high-fat meals (500 mg of ceritinib)					
	F	27	6930		
$AUC_{0-\infty}$ (ng·h/mL)	LF	14	10 900	LF/F	1.58 (1.34-1.86)
	HF	14	12 000	HF/F	1.73 (1.46-2.05)
	F	27	160		
C_{max} (ng/mL)	LF	14	229	LF/F	1.43 (1.21-1.71)
	HF	14	225	HF/F	1.41 (1.18-1.68)
Food effect of light snack (750 mg of ceritinib)					
$AUC_{0-\infty}$ (ng·h/mL)	F	12	9390		
	LS	12	14 500	LS/F	1.54 (1.19-1.99)
C_{max} (ng/mL)	F	12	213		
	LS	12	308	LS/F	1.45 (1.15-1.82)

$AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CL/F, apparent oral clearance; F, fasting conditions; HF, high-fat meal; LF, low-fat meal; LS, light snack; n, number of evaluable subjects; $t_{1/2}$, terminal elimination half-life; t_{max}, time to peak plasma concentration; V_z/F, apparent volume of distribution.

Novartis Pharmaceuticals) or multiple dosing.[9–11] The frequency of specific all-grade GI AEs, such as diarrhea and nausea, appeared to be dose related (Table 3). The incidence of diarrhea was 21.4% at 500 mg fasted and 33.3% at 750 mg fasted. The incidence of nausea was 10.7% at 500 mg fasted and 25.0% at 750 mg fasted.

The overall tolerability of ceritinib at the 500-mg dose level appeared to be improved with food (Table 3). Under fasting conditions, ceritinib 500 mg was reasonably well tolerated (46.4% subjects with AEs), whereas under fed conditions, fewer subjects experienced AEs (25.0% subjects with AEs). A similar trend was not observed at ceritinib 750 mg, in which 41.7% subjects had AEs with or without food.

Diarrhea was reported by some subjects who received ceritinib 500 mg under fasting conditions (21.4%); however, the incidence was decreased when ceritinib was administered with food (10.7%). A similar trend was observed for nausea as well at the same dose level (10.7% and 3.6%, with and without food, respectively). At ceritinib 750 mg, the incidence of diarrhea was the same with or without food (33.3%). However, the incidence of nausea was reduced when ceritinib was administered with food (25% without food vs none with food). No subjects experienced vomiting across dose and prandial conditions.

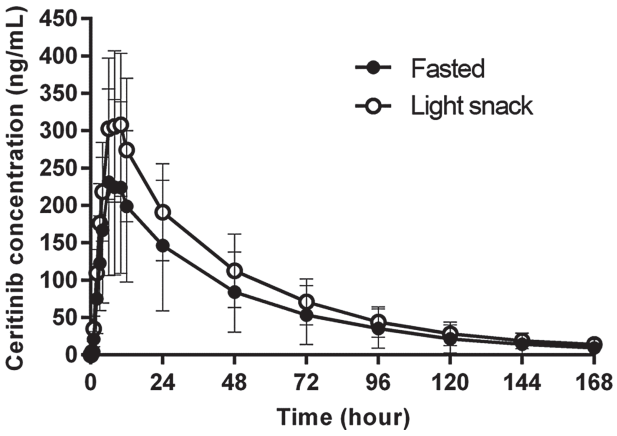

Figure 2. Linear plot of plasma ceritinib after a single oral 750 mg dose under fasting conditions or with a light snack. Data are presented as arithmetic mean (±SD).

Discussion

In recent years, there has been considerable interest in understanding the effect of food intake on the oral bioavailability of molecularly targeted oncology therapies, mostly TKIs.[17,18] On the basis of ceritinib's low solubility, low permeability, and low extent of metabolism based on the amount of unchanged drug recovered in the feces,[10–12] ceritinib can be classified as a class 4 drug in the Biopharmaceutics Classification System[19] and the Biopharmaceutical Drug Disposition Classification System.[20] It is well documented that the presence of food within the GI tract can alter the bioavailability of drugs by various means, including stimulation of bile flow, modification of gastric motility patterns, GI pH change, alteration in splanchnic blood flow, alteration in presystemic metabolism, and physical/chemical interactions with the drug.[15,21] As noted by Custodio et al,[20] an increase in bioavailability in the presence of a high-fat meal is more likely to occur for a class 4 drug due to increased solubilization of the drug in the intestine. Based on our single-dose food-effect study results, a high-fat meal increased the C_{max} (90%CI) and $AUC_{0-\infty}$ (90%CI) of ceritinib by 41% (18%, 68%) and 73% (46%, 105%), respectively, while a low-fat meal increased the C_{max}

Table 3. Total and Specific Gastrointestinal Adverse Events by Dose and Prandial Condition in Food-Effect Studies Conducted in Healthy Subjects

	Ceritinib Dose			
Preferred Term	500 mg (Fasted) N = 28, n (%)	500 mg (Fed) N = 28, n (%)	750 mg (Fasted) N = 12, n (%)	750 mg (Fed) N = 12, n (%)
Any adverse event (AE)				
Total	13 (46.4)	7 (25.0)	5 (41.7)	5 (41.7)
Specific gastrointestinal AEs				
Diarrhea	6 (21.4)	3 (10.7)	4 (33.3)	4 (33.3)
Nausea	3 (10.7)	1 (3.6)	3 (25.0)	0
Vomiting	0	0	0	0

A subject with multiple occurrences of an AE under 1 treatment is counted only once in the AE category for that treatment.

(90%CI) and $AUC_{0-\infty}$ (90%CI) by 43% (21%, 71%) and 58% (34%, 86%), respectively, as compared with the fasted state (Table 2). Because the 90%CIs of the geometric mean ratio of both C_{max} and $AUC_{0-\infty}$ were outside the bioequivalence range of 0.8 to 1.25, bioequivalence between the fasting and the fed conditions could not be established.

Although the enhancement of ceritinib absorption was shown to be more pronounced with a high-fat meal as compared to a low-fat meal, the difference is not considered substantial in that an increase in fat content from 9 g (low-fat meal) to 58 g (high-fat meal) led to only a 15% difference in ceritinib $AUC_{0-\infty}$. To further evaluate if fat content had an impact on the extent of ceritinib absorption, a study with a light snack (1.5 g fat) was subsequently performed. It was found that even a very low-fat meal (light snack) could lead to clinically important ceritinib exposure changes with C_{max} (90%CI) and $AUC_{0-\infty}$ (90%CI) of ceritinib increased by 45% (15%, 82%) and 54% (19%, 99%), respectively, similar to the extent of increase caused by a low-fat meal as described above. Accordingly, food intake has a consistent positive effect on ceritinib absorption, even when meals include a very low fat content. On the basis of the observations from both food-effect studies, the improved absorption of ceritinib in the fed state is speculated to be due to the enhanced bile salt secretion in the postprandial intestine, which leads to increased micellar solubilization and wetting of the drug, both of which can enhance the dissolution rate of the drug.[21,22]

It has been reported that food intake may improve the GI tolerability of TKIs such as imatinib and bosutinib. Imatinib does not exhibit a food effect; thus, it is recommended that the drug be taken with food to minimize GI irritation.[13] In a food-effect trial, a high-fat meal increased bosutinib exposure by 2-fold. Bosutinib showed better tolerability when coadministered with food;[14,23] as a result, bosutinib was coadministered with a meal in patient trials and is advised to be taken once daily with food.[23,24] At the recommended ceritinib dose of 750 mg administered under fasting conditions, all grade GI symptoms primarily manifested as diarrhea, nausea, vomiting, or abdominal pain and occurred in 86%, 80%, 60%, and 54%, respectively, of 255 patients enrolled in the phase 1 dose-escalation and expansion study.[10] Given the known safety profile of ceritinib, it is of interest to determine if the observed improved GI tolerability of other multikinase inhibitors in the presence of food also applies to ceritinib.

As shown in the food-effect studies, the number of healthy subjects reporting AEs at the 500 mg dose level appeared to be lower with food despite a >50% increase in single-dose ceritinib $AUC_{0-\infty}$ (Table 3). The incidence of individual GI symptoms, such as diarrhea and nausea, was also reduced with food at the same dose level. A similar trend in overall AEs and diarrhea was not seen at 750 mg. These results suggest that food intake improves the tolerability of a single dose of ceritinib; however, the effect seems to be dose related. There also appears to be a dose dependency regarding the frequency of GI AEs when ceritinib was administered under fasting conditions. However, exposure-safety analyses using data from patients with ALK-positive cancer suggested that no apparent trend was identified between systemic exposure (as assessed by average steady-state C_{trough}) and grade 3-4 GI AEs,[12,25] suggesting that the majority of GI AEs could be due to the high ceritinib concentration in the gut, which directly leads to GI AEs. In light of these findings, GI tolerability may be affected by both dose and food.

Despite the potential benefit of improved GI tolerability with food, it needs to be highlighted that the recommended daily ceritinib dose of 750 mg taken under fasting conditions is the highest dose tested in clinical studies thus far. Ceritinib at a dose of 750 mg taken with a meal is expected to result in systemic exposure exceeding that of a 750 mg ceritinib dose taken fasted and may increase exposure-dependent adverse drug reactions.[10] It has been observed that increasing systemic exposure is associated with a higher incidence of grade 3 ALT and AST elevations,[25] one of the most common treatment-related non-GI AEs. Therefore, the current US prescribing information recommends that ceritinib be taken on an

empty stomach (ie, do not administer within 2 hours of a meal).[10] This suggests that dosing with food will likely require the use of a dose lower than 750 mg, taking into account the >50% increase in ceritinib $AUC_{0-\infty}$ in the presence of food after a single-dose administration of ceritinib. However, the magnitude of the food effect observed after a single dose does not necessarily translate to that observed under repeated dosing conditions.

A different food effect has been observed with another ALK inhibitor, alectinib, in which after a single oral administration of 300 mg in patients with ALK-positive NSCLC immediately after a meal, both C_{max} and AUC increased by 1.8-fold as compared with the fasted state.[26] On the other hand, after dosing at 300 mg twice daily, the C_{max} and AUC were comparable under fasting and fed conditions.[26,27] Similarly, the effects of food on the PK of the farnesyltransferase inhibitor lonafarnib after single-dose administration diminished on multiple doses.[28] This observation is postulated to be attributed to mechanisms such as enzyme and/or efflux transporter saturation and autoinhibition of drug-metabolizing enzymes that lead to temporal reduction in drug clearance.[28] We have previously investigated the PK of ceritinib following single-dose and once-daily dosing in patients with ALK-positive cancer.[10–12] Ceritinib also displays nonlinear PK over time, with reduced CL/F from the first dose (88.5 L/h) to steady state on cycle 2 day 1 after 3 weeks of daily dosing (33.2 L/h). The likelihood of ceritinib saturating cytochrome P450 3A (CYP3A) and P-gp at clinically achievable concentration is low, as the unbound C_{max} (0.05 μM at 750 mg steady state) is well below the unbound K_m (0.279 μM) for ceritinib presystemic metabolism via CYP3A pathway,[12] and the low solubility of ceritinib[10,12] limits the concentration into the enterocytes, likely preventing saturation of P-gp. However, as ceritinib is a substrate as well as a time-dependent inhibitor of CYP3A, it is likely that the PK nonlinearity could be attributed to autoinhibition of CYP3A, and a diminished food effect of ceritinib at steady state is plausible.

In order to determine the food effect of ceritinib under a repeated-dosing regimen and to identify a ceritinib dose taken with food to improve GI tolerability in patients, a 3-arm randomized, open-label, PK and safety trial is currently being conducted to evaluate lower doses (450 mg or 600 mg) of ceritinib taken with food that provides similar steady-state systemic exposure to that of the 750 mg dose taken under fasting conditions in patients with ALK-positive NSCLC after repeated dosing.[25,29] Practical considerations, such as differing patterns of food intake among individual patients that may contribute to interpatient and intrapatient variability in bioavailability, can also be properly evaluated in a clinical setting.

In summary, although administration of ceritinib with food may enhance GI tolerability, consumption of a meal even with a very low-fat content markedly increases the oral bioavailability of ceritinib. A randomized trial is ongoing to evaluate an alternative way to give ceritinib (lower doses with food) that may lead to better GI tolerability in patients with ALK-positive NSCLC while maintaining similar steady-state exposure.

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Disclosures

Y.Y.L., W.G., T.L., and D.S. contributed to conception and design. All authors were provided inputs for data analysis and interpretation, were involved in manuscript writing, and approved the final draft of the manuscript.

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