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Phase 1 Study Evaluating the Effects of the Proton Pump Inhibitor Rabeprazole and Food on the Pharmacokinetics of Lorlatinib in Healthy Participants

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Abstract

Lorlatinib is approved worldwide as treatment for *anaplastic lymphoma kinase*-positive and *c-ros oncogene 1*-positive non-small cell lung cancer. The objectives of this phase 1, open-label crossover study (NCT02569554) in healthy adult participants were to determine (1) the effects of the proton pump inhibitor (PPI) rabeprazole on lorlatinib pharmacokinetics (PK), (2) the effects of a high-fat meal on lorlatinib PK, and (3) the relative bioavailability of an oral solution to tablet formulation of lorlatinib under fasted conditions. Participants were followed on-study for ≥50 days after the first dose of lorlatinib. Participants received treatments over 4 periods, with a washout of ≥10 days between consecutive lorlatinib doses. Twenty-seven participants were enrolled and received lorlatinib, and all were assessed for PK and safety. Results showed no effect of multiple doses of rabeprazole on the total plasma exposure of a single oral dose of lorlatinib 100-mg tablets. The results also indicated that a high-fat meal had no effect on lorlatinib PK after a single 100-mg oral dose. In addition, the relative bioavailability of lorlatinib oral solution compared with lorlatinib tablets was complete (approximately 108%). The safety profile of lorlatinib was consistent with that reported in previous studies, and most treatment-related adverse events were mild to moderate. These data indicate that lorlatinib can be administered with drugs that modify gastric acid, including PPIs, without restriction. These results also confirm that lorlatinib can be administered regardless of food intake.

Keywords

drug-drug interactions, drug-food interactions, food effect, lorlatinib, pharmacokinetics and drug metabolism, proton pump inhibitor, rabeprazole

Small-molecule tyrosine kinase inhibitors (TKIs) of anaplastic lymphoma kinase (ALK) are used to treat patients with advanced or metastatic non-small cell lung cancer (NSCLC) that is positive for chromosomal arrangements involving the *ALK* gene.[1] In this distinct subtype of NSCLC,[2] ALK TKIs offer significant

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benefits versus conventional chemotherapy.[3–6] Crizotinib is a first-line TKI used to treat patients with *ALK*-positive and *c-ros oncogene 1* (*ROS1*)-positive NSCLC, and lorlatinib (Lorbrena®, Pfizer Inc., New York, New York) is a third-generation TKI of ALK and ROS1.

Human absorption, distribution, metabolism, and excretion studies have found that lorlatinib is primarily metabolized by oxidation (*N*-demethylation, *N*-oxidation) and by *N*-glucuronidation.[7] Lorlatinib exhibited relatively fast absorption (time to maximum concentration [T_{max}] of around 1-2 hours) and biexponential postpeak decline, with a mean terminal plasma elimination half-life ($t_{1/2}$) of about 20 hours.[7] Geometric mean maximum plasma concentration (C_{max}) was about 600 ng/mL, and geometric mean overall exposure in plasma (AUC_{inf}) ranged from 7700 to 8500 ng·h/mL following administration of 100 mg/100 μCi [^{14}C]lorlatinib. Urinary excretion of unchanged lorlatinib was found to be low (~0.7%), as was renal clearance (1.6 mL/min).[7] Lorlatinib is predominantly metabolized by the cytochrome P450 (CYP) CYP3A4 and by UDP-glucuronosyltransferase (UGT) 1A4.[8] Coadministration of lorlatinib with the strong CYP3A inhibitor, itraconazole, increased the plasma exposure of lorlatinib in healthy participants.[9]

Lorlatinib was designed to penetrate the blood-brain barrier, and an in vitro study found that lorlatinib had greater inhibitory effects than crizotinib on immortalized human brain microvascular endothelial cells and also increased brain permeability in rats.[10–13] In a murine study, it was found that lorlatinib brain accumulation was inhibited by P-glycoprotein, and in another murine model it was shown that simultaneous administration with elacridar, a P-glycoprotein inhibitor, increased absolute brain levels of lorlatinib.[14,15] In these same murine models, CYP3A4 activity restricted the oral availability of lorlatinib, and ritonavir, a CYP3A4 inhibitor, reversed this effect on bioavailability and further increased brain levels of lorlatinib.[14,15]

Lorlatinib and other approved ALK TKIs are administered orally, a route with inherent risk of potential impact on drug absorption by food or other factors that could alter the environment of the gastrointestinal tract.[8] Because lorlatinib is orally administered, it is critical to evaluate the effect of food on lorlatinib pharmacokinetics (PK) to determine if any recommendations regarding the timing of food need to be provided for clinical use of lorlatinib. Many patients with NSCLC receive concomitant proton pump inhibitors (PPIs) or other gastric acid-modifying agents (eg, histamine H_2 receptor antagonists or locally acting antacids). Agents that elevate gastric pH can potentially reduce the absorption of drugs with higher solubility at acidic pH, resulting in lowered plasma concentrations, which may in turn impact the efficacy of those drugs.[8] Hence, an assessment of the effect of PPIs, which have the strongest and most long-lasting effect on suppression of gastric acid of all antacid classes, on lorlatinib PK was warranted.

In vitro studies of lorlatinib have shown that both the acetate and freebase forms of lorlatinib have pH-dependent solubility, with aqueous solubility >10 mg/mL at pH <2 and 0.1 mg/mL at pH 7.7. Thus, coadministration with gastric acid-reducing agents may potentially reduce gastrointestinal absorption of lorlatinib.[8]

This phase 1 study (NCT02569554) was conducted to evaluate the effect of gastric acid-reducing agents on lorlatinib PK and to evaluate the impact of a high-fat meal to demonstrate the lack of effect of food on lorlatinib PK. Although lorlatinib is predominantly metabolized by CYP3A4/5 and by UGT1A4, CYP2C19 is also involved in its metabolism. PPIs such as omeprazole and rabeprazole have differing levels of inhibitory effect on CYP3A4 and CYP2C19, with rabeprazole demonstrating the lowest inhibitory potency.[16–18] Rabeprazole was therefore selected as the probe PPI in this study. The selection of a high-fat meal in this study was intended to evaluate the greatest potential effect of food on lorlatinib PK. This study was also designed to assess the relative bioavailability of a lorlatinib oral solution, which was included to gain a better understanding of the dissolution and absorption of lorlatinib from the solid-tablet dosage form.

Methods

This study was sponsored by Pfizer Inc. and conducted at a Pfizer Clinical Research Unit in Brussels, Belgium. The study protocol and participant consent form were approved by the Independent Ethics Committee (Comite d'ethique Hospitalo-Facultaire Erasme ULB) at the clinical research unit where the study was conducted.

Study Participants

All participants provided written informed consent prior to study participation. The study was conducted in compliance with Good Clinical Practice, guidelines of the International Conference on Harmonization, and the Declaration of Helsinki. In addition, all local regulatory requirements were followed, especially those affording greater protection and safety for trial participants.

Eligible participants were healthy adults (female of nonchildbearing potential or male) aged 18-55 years with a body mass index of 17.5-30.5 kg/m^2 and no evidence or history of significant hematologic, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic

disease. Participants were excluded for the following reasons: conditions affecting drug absorption; use of tobacco/nicotine products within 90 days of screening; history of regular alcohol consumption within 6 months of screening; treatment with investigational drugs within 30 days or 5 half-lives of the first dose of lorlatinib, whichever was longer; prescription or nonprescription drugs or supplements within 7 days or 5 half-lives, whichever was longer, except acetaminophen/paracetamol; resting supine blood pressure ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic); supine 12-lead electrocardiogram corrected QT interval (QTc) >450 milliseconds or QRS interval > 120 milliseconds; aspartate aminotransferase/serum glutamic oxaloacetic transaminase or alanine aminotransferase/serum glutamic pyruvic transaminase above the upper limit of normal (ULN); or total bilirubin ≥ 1.5 ULN. In addition, herbal supplements and hormone-replacement therapy must have been discontinued ≥ 28 days prior to the first dose of study medication.

Table 1. Demographics and Baseline Characteristics

Characteristic	Total (n = 27)
Sex (male), n (%)	26 (96.3)
Age (years), mean (SD)	35.9 (10.3)
Range	20-55
Age, n (%)	
<14 years	0 (0)
14-44 years	21 (77.8)
45-64 years	6 (22.2)
≥65 years	0
Race, n (%)	
White	21 (77.8)
Black	6 (22.2)
Weight (kg), mean (SD)	78.2 (12.5)
Range	57.4-101.5
Height (cm), mean (SD)	176.6 (6.8)
Range	159-190
BMI (kg/m^2), mean (SD)	25.0 (3.3)
Range	18.7-30.0

BMI, body mass index; SD, standard deviation.

Study Design

This was a phase 1, open-label crossover study in healthy participants. The primary objectives were to (1) evaluate the effects of multiple doses of rabeprazole on the PK of a single 100-mg oral dose of lorlatinib tablets under fasted conditions, (2) evaluate the effects of a high-fat meal on the PK of a single 100-mg oral dose of lorlatinib tablets, and (3) estimate the relative bioavailability of a single 100-mg oral dose of lorlatinib solution under fasted conditions. The secondary objective was to assess the safety and tolerability of lorlatinib in this population.

Drug Administration and Treatment

The study had a 4-period, 4-sequence design. The treatments were:

- Treatment A (reference)—a single dose of lorlatinib 100 mg (4 × 25-mg tablets) administered in a fasted state;
- Treatment B—a single dose of lorlatinib 100 mg (4 × 25-mg tablets) administered following a high-fat meal;
- Treatment C—once-daily rabeprazole 20 mg (2 × 10-mg tablets) administered in the evening on days 1-5 and a single dose of lorlatinib 100 mg (4 × 25-mg tablets) administered on the morning of day 6 in a fasted state;
- Treatment D—a single dose of lorlatinib 100 mg (100 mL of 1 mg/mL oral solution) administered in a fasted state.

This clinical study used a single dose of lorlatinib 100 mg. Based on safety data from prior studies conducted in participants administered lorlatinib 100 mg,[10,19] 4 lorlatinib 100-mg single doses administered at least 10 days apart were expected to pose little risk to healthy adults. All treatments were to be administered in the morning after an overnight fast of at least 10 hours with ambient temperature water to a total volume of 240 mL. All tablets were to be swallowed whole without manipulation or chewing.

The total calorific content of the high-fat meal during treatment B was approximately 50% fat; the approximately 1000 calories included 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories as recommended by the US Food and Drug Administration. This breakfast, provided at the clinical research unit, was to be consumed within 25 minutes and completed 5 minutes before lorlatinib dosing.

During treatment C, rabeprazole was administered in the evening, staggered from the morning administration of lorlatinib, to further minimize the potential impact of rabeprazole on lorlatinib PK through the inhibition effect of rabeprazole on CYP enzymes. Participants were instructed to self-administer rabeprazole according to administration instruction provided by the sponsor.

Each participant was to receive all treatments (A to D) over 4 periods, with a washout of ≥10 days between successive doses of lorlatinib. Participants were planned to be evenly distributed among 4 sequences: (ABCD, BCDA, CDAB, or DABC); see Supplemental Table S1 for details. Participants were followed for ≥50 days after the first dose of lorlatinib through study completion. To standardize the conditions on PK sampling days, all participants were required to refrain from lying down (except when required for blood pressure, pulse

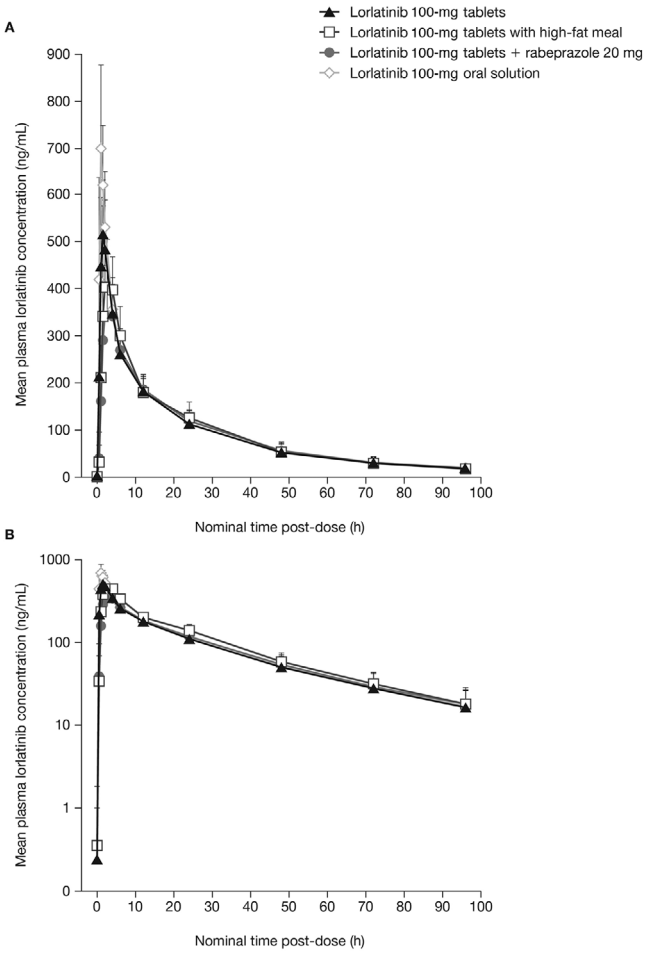

Figure 1. Mean plasma lorlatinib concentration-versus-time profiles following single oral doses. (A) Linear plot. (B) Semilogarithmic plot.

Table 2. Summary of Plasma Lorlatinib Pharmacokinetic Parameters Following a Single Oral Dose

Parameter, Unit[a]	Treatment A Lorlatinib 100-mg Tablets (n = 24)	Treatment B Lorlatinib 100-mg Tablets + High-Fat Meal (n = 23)	Treatment C Lorlatinib 100-mg Tablets + Rabeprazole 20 mg (n = 23)	Treatment D Lorlatinib 100-mg Oral Solution (n = 24)
Geometric mean AUC_{inf}, ng·h/mL	8712 (24)	8779 (24)	8629 (24)	9359 (24)
Arithmetic mean AUC_{inf}, ng·h/mL	8959 ± 2382.7	9031 ± 2281.8	8883 ± 2428.1	9617 ± 2437.5
Geometric mean AUC_{last}, ng·h/mL	8191 (21)	8262 (22)	8011 (21)	8789 (21)
Arithmetic mean AUC_{last}, ng·h/mL	8382 ± 1992	8460 ± 1939	8192 ± 1927	8986 ± 2040
Geometric mean C_{max}, ng/mL	548 (20)	489 (26)	383 (28)	705 (22)
Arithmetic mean C_{max}, ng/mL	559 ± 115	505 ± 144	398 ± 114	722 ± 185
T_{max}, h	1.5 (0.5-2.0)	2.0 (1.0-6.0)	2.0 (1.5-6.0)	1.0 (0.5-1.5)
Arithmetic mean $t_{1/2}$, h	24.2 ± 5.2	23.7 ± 6.0	25.6 ± 6.4	24.1 ± 5.4
Geometric mean CL/F, L/h	11.5 (24)	11.4 (24)	11.6 (24)	10.7 (24)
Arithmetic mean CL/F, L/h	11.8 ± 2.5	11.7 ± 2.8	11.9 ± 2.5	11.0 ± 2.4

%CV, percent coefficient of variation; AUC_{inf}, area under the plasma concentration-versus-time curve from time 0 to infinity; AUC_{last}, area under the plasma concentration-versus-time curve from time 0 to the time of the last quantifiable concentration; CL/F, apparent oral plasma clearance; C_{max}, maximum observed plasma concentration; SD, standard deviation; $t_{1/2}$, terminal plasma half-life; T_{max}, time to C_{max}.

[a] Data are presented as either geometric mean (geometric %CV) or arithmetic mean ± SD for all except median (range) for T_{max}.

Table 3. Summary of Treatment Comparisons for Lorlatinib

Parameter, Unit	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90%CI for Ratio
	Test	Reference		
Lorlatinib 100-mg tablets + high-fat meal (test) versus 100-mg tablets (reference)				
AUC_{inf}, ng·h/mL	8874	8473	104.7	101.3-108.3
AUC_{last}, ng·h/mL	8347	7980	104.6	101.3-108.1
C_{max}, ng/mL	484.5	533.1	90.9	84.8-97.4
Lorlatinib 100-mg tablets + rabeprazole 20-mg (test) versus 100-mg tablets (reference)				
AUC_{inf}, ng·h/mL	8547	8473	100.9	97.6-104.3
AUC_{last}, ng·h/mL	7952	7980	99.7	96.5-102.9
C_{max}, ng/mL	377.0	533.1	70.7	66.0-75.8
Lorlatinib 100-mg oral solution (test) versus 100-mg tablets (reference)				
AUC_{inf}, ng·h/mL	9141	8473	107.9	104.4-111.5
AUC_{last}, ng·h/mL	8602	7980	107.8	104.4-111.3
C_{max}, ng/mL	691.5	533.1	129.7	121.2-138.9

AUC_{inf}, area under the plasma concentration-versus-time curve from time 0 to infinity; AUC_{last}, area under the plasma concentration-versus-time curve from time 0 to the time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration.
[a] Ratios and 90%CIs are expressed as percentages.

rate, and electrocardiogram measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

PK Assessments

Blood samples for lorlatinib PK assessments were collected at 0 hours (predose) and 0.5, 1, 1.5, 2, 4, 6, 12, 24, 48, 72, and 96 hours after lorlatinib administration in each treatment period. Plasma lorlatinib concentrations were measured using a validated high-performance liquid chromatography-tandem mass spectrometry method at Covance Bioanalytical Services (Shanghai, China).[20]

Standard noncompartmental analysis was used to obtain estimates for the following lorlatinib plasma PK parameters: area under the plasma concentration-versus-time curve from time 0 to infinity (AUC_{inf}), AUC from time 0 to the time of the last quantifiable concentration (AUC_{last}), C_{max}, T_{max}, $t_{1/2}$, and apparent oral plasma clearance (CL/F). PK parameter values were calculated using an internally validated software system (eNCA v2.2.4). Samples below the lower limit of quantification were set to 0 ng/mL for the PK analysis. Actual sample collection times were used for the PK analysis.

Safety Assessments

Participants were assessed for safety, which included physical examinations, laboratory tests, electrocardiogram, concomitant medication, and frequency and severity of adverse events (AEs).

Statistical Analysis

The prespecified primary lorlatinib PK end points were AUC_{inf} and C_{max}. Secondary PK end points included lorlatinib AUC_{last}, T_{max}, $t_{1/2}$, and CL/F. The PK concentration population included all participants who received ≥1 dose of lorlatinib; the PK parameter population included all participants who received ≥1 dose of lorlatinib and had ≥1 estimated PK parameter. The safety population included all participants who received ≥1 dose of study medication.

Statistical analysis for the evaluation of the effect of food and the effect of PPIs, and for the estimation of the relative bioavailability of the lorlatinib oral solution to the tablet formulation, was conducted by subjecting the estimated lorlatinib AUC_{inf}, C_{max}, and AUC_{last} to a mixed-effects model with sequence, period, and treatment as fixed effects and participant within sequence as a random effect. Adjusted mean differences and 90% confidence intervals (CIs) for the differences were exponentiated to provide estimates of the ratios of adjusted geometric means (test/reference) and 90%CIs for the ratios. Lack of effect was to be concluded if the 90%CIs for the ratio of adjusted geometric means for both AUC_{inf} and C_{max} fell within bioequivalence criteria of 80% to 125%. All other PK parameters were summarized descriptively.

Results

Participants

Twenty-seven participants were enrolled and received lorlatinib, and all were assessed for PK and safety

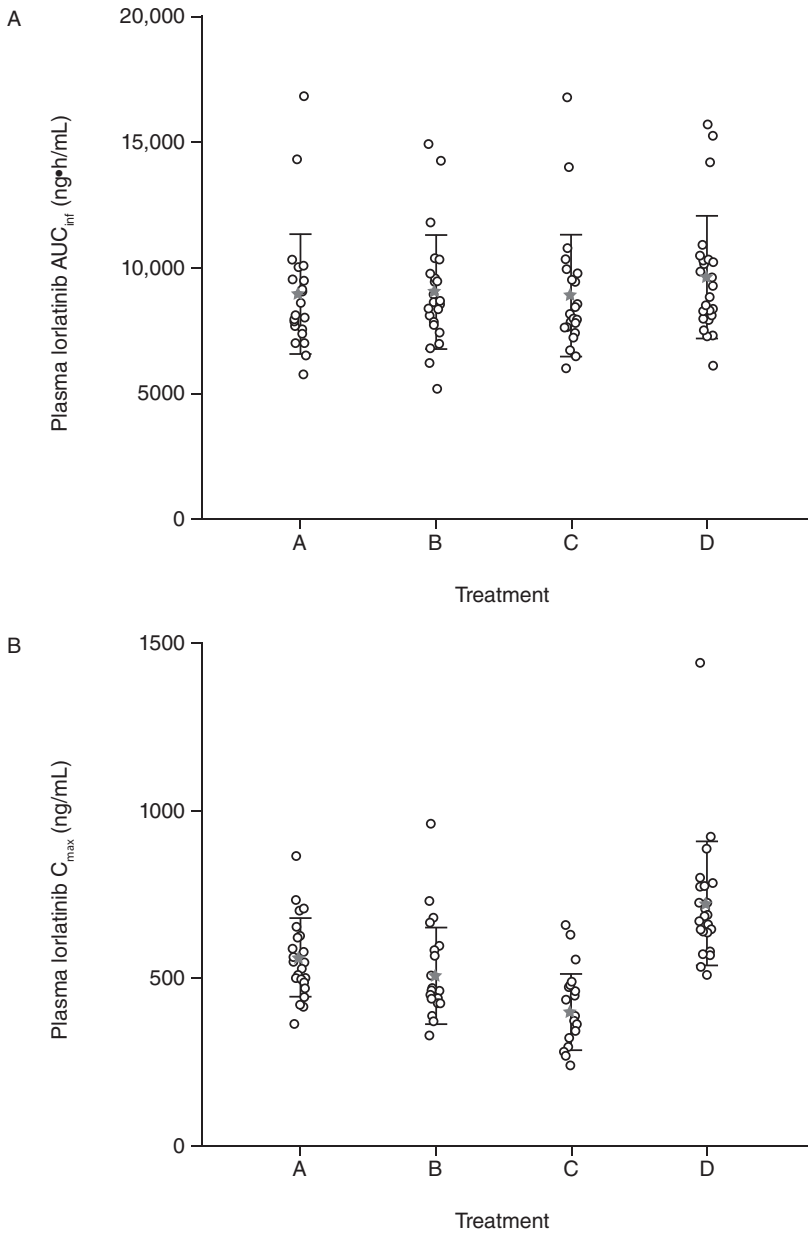

Figure 2. Individual and mean plasma lorlatinib AUC_{inf} (A) and C_{max} (B). Stars represent the arithmetic means, the open circles represent individual values, and the bars are the standard deviations. AUC_{inf}, area under the plasma concentration-versus-time curve from time 0 to infinity; C_{max}, maximum observed plasma concentration.

(Supplemental Table S2). Five participants discontinued because of AEs (n = 3) or not meeting re-entry criteria for the next study period (n = 2). Most participants were male and white (Table 1).

Plasma Pharmacokinetics

Twenty-four participants who contributed to the PK analysis and the number of participants for each treatment period are provided in Supplemental Table S2. The mean plasma concentration-versus-time profiles of lorlatinib following single oral doses in these groups are shown in Figure 1. Descriptive statistics of PK parameters for lorlatinib are summarized in Table 2. Lorlatinib peak plasma concentrations, based on median T_{max}, were achieved within 2 hours for all participants who received lorlatinib alone in a fasted state. After C_{max} was reached, lorlatinib concentrations decreased in parallel across treatment groups, indicating no differences in the lorlatinib terminal elimination rate across the treatments evaluated in this study: mean $t_{1/2}$ was 24.2 hours for the reference lorlatinib tablets administered in a fasted state, 23.7 hours for lorlatinib

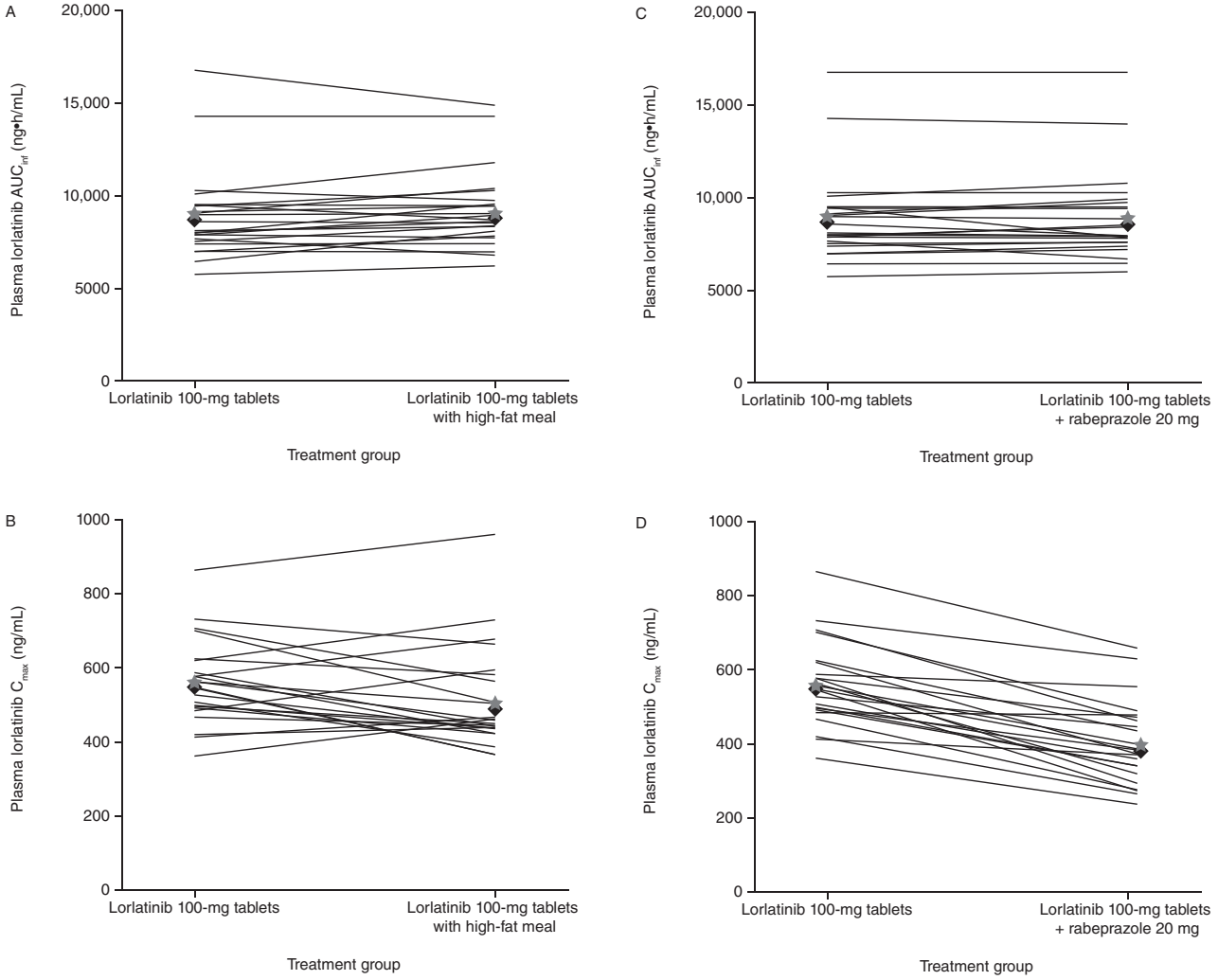

Figure 3. Individual plasma lorlatinib plots of AUC_{inf} and C_{max} for lorlatinib 100-mg tablets versus lorlatinib 100-mg tablets + a high-fat meal (A and B) and lorlatinib 100-mg tablets versus lorlatinib + rabeprazole 20 mg (C and D). Diamonds represent the geometric mean, and stars represent the arithmetic mean. AUC_{inf}, area under the plasma concentration-versus-time curve from time 0 to infinity; C_{max}, maximum observed plasma concentration.

tablets with a high-fat meal, 25.6 hours for lorlatinib tablets with rabeprazole, and 24.1 hours for lorlatinib administered as an oral solution in a fasted state.

Results from the statistical analyses for the study objectives are summarized in Table 3. The 90%CI around the estimated geometric mean ratios for lorlatinib given with a high-fat meal versus the fasted state for both AUC_{inf} and C_{max} fell within 80%-125%, indicating that food does not have an effect on the PK of lorlatinib. Similarly, the 90%CI around the geometric mean ratio for lorlatinib AUC_{inf} given with rabeprazole versus lorlatinib alone fell within 80%-125%, but a 29% decrease (90%CI, 24%-34%) in geometric mean C_{max} was observed. Plots for lorlatinib AUC_{inf} and C_{max} are presented in Figure 2. Individual, geometric mean, and arithmetic mean lorlatinib AUC_{inf} and C_{max} values with and without food and with and without rabeprazole are plotted as matchstick plots in Figure 3. The plots show that lorlatinib C_{max} was reduced by rabeprazole treatment; however, no change in lorlatinib AUC_{inf} was noted across the different treatments.

The bioavailability of the lorlatinib oral solution relative to the tablet formulation was 108% (90%CI, 104%-112%). About a 30% higher C_{max} (90%CI, 21%-39%) was achieved with the oral solution than with the tablet formulation.

Safety and Tolerability

Most participants in each treatment period experienced AEs, and most AEs were considered related to treatment (Table 4). The majority of AEs

Table 4. Summary of Adverse Events

	Treatment A Lorlatinib 100-mg Tablets (n = 24)	Treatment B Lorlatinib 100-mg Tablets + High-Fat Meal (n = 23)	Treatment C Lorlatinib 100-mg Tablets + Rabeprazole 20 mg (n = 23)	Treatment D Lorlatinib 100-mg Oral Solution (n = 24)
Participants with any treatment-emergent AE, n (%)	19 (79)	15 (65)	19 (83)	16 (67)
Participants with any treatment-related AE, n (%)	19 (79)	15 (65)	19 (83)	16 (67)
Participants with any serious treatment-related AE, n (%)	0	0	0	0
Treatment-related AEs occurring in ≥10% of participants in any group, n (%)				
Headache	7 (29)	4 (17)	7 (30)	6 (25)
First-degree AV block	5 (21)	2 (9)	4 (17)	3 (13)
Acne	4 (17)	2 (9)	2 (9)	4 (17)
Diarrhea	3 (13)	1 (4)	2 (9)	2 (8)

AE, adverse event; AV, atrioventricular block.

(119 of 135) were mild in severity, and the remainder were considered moderate. No participants had serious or severe treatment-related AEs. The most common treatment-related AEs (occurring in ≥10% of participants in any group) were headache, first-degree atrioventricular (AV) block, acne, and diarrhea. Two participants discontinued from the study because of treatment-related first-degree and second-degree AV block, which was noted at the time the participants returned after a washout prior to the next study period. The participant with the first-degree AV block had a history of an intermittent AV block, which was unknown prior to dosing; the AE started 0.8 hours after day 1 lorlatinib dosing and had not resolved as of the last follow-up (>62.6 hours). The second-degree AV block in the second participant resolved on the same day it was detected. One participant discontinued because of tonsillitis that was not considered related to the study treatment. There were no deaths during the study.

Discussion

The definitive food-effect evaluation conducted in this study indicated that a high-fat meal did not have an effect on the PK of a single oral dose of lorlatinib 100 mg. A previous pilot of the effect of food conducted in an earlier first-in-human phase 1 trial in patients with advanced *ALK*-positive or *ROS1*-positive NSCLC provided similar results.[19]

Results from this study also indicate that lorlatinib can be administered in combination with all classes of acid-reducing agents. Although lorlatinib C_{max} was decreased by 29% when lorlatinib was given with the PPI rabeprazole, total lorlatinib plasma exposure (AUC_{inf}) was not affected by coadministration of rabeprazole. Because coadministration with rabeprazole, which belongs to the most potent class of acid-reducing agents (the PPIs),[16] did not change lorlatinib plasma exposure, it is rational that less potent and shorter-acting acid-reducing agents (such as H_2 antagonists and locally acting antacids) would also not affect lorlatinib total exposure when coadministered with lorlatinib.

The relative timing of administration of lorlatinib and rabeprazole was staggered to minimize the potential increase of lorlatinib plasma concentration because of metabolic inhibition by rabeprazole, which could confound the effect of rabeprazole on lorlatinib absorption. Because the effect of most PPIs on the gastric pH is long-acting and high gastric pH is maintained over a 24-hour period after continued PPI administration, the design of the study with PPI dosing in the evening and lorlatinib dosing in the morning would best allow for characterizing the effect of rabeprazole on lorlatinib absorption. Also, because the effect of food or PPI on PK would be the greatest under the study conditions, no food or PPI effect on lorlatinib PK is expected for persons taking multiple, chronic doses of lorlatinib. Therefore, the results from this study are intended to support the recommendation for lorlatinib to be given orally without regard to food or concurrent use of acid-reducing agents.

Because solutions are more readily absorbed after oral administration than with tablet formulations, which require disintegration and dissolution of the drug from the solid dosage form (tablet), higher C_{max}

and shorter T_{max} were expectedly observed with an oral solution of lorlatinib than with administration of the tablet. The lorlatinib AUC_{inf} following administration of an oral solution was equivalent to that of the tablet formulation, indicating that lorlatinib from the tablet formulation is quickly and nearly completely absorbed.

The safety profile of lorlatinib was consistent with the safety data observed in previous studies in that most treatment-related AEs were mild to moderate.[10,19] There were no serious AEs, dose reductions, or deaths. Two participants discontinued from the study because of moderate, treatment-related AV block. Although in 1 participant the AE had not resolved as of last follow-up, in the other participant the AE started and resolved on the same day. There were no clinical sequelae, and exposure in subsequent study periods was avoided. AV block is a known adverse effect of lorlatinib.[11]

Conclusions

There was no effect of multiple doses of rabeprazole on the plasma exposure of lorlatinib following a single oral 100-mg dose under fasted conditions. A high-fat, high-calorie meal similarly had no effect on the PK of lorlatinib, and thus, lorlatinib can be administered regardless of food intake. Coadministration of lorlatinib with rabeprazole 20 mg decreased peak exposure (C_{max}) by approximately 30% relative to lorlatinib tablets alone. The relative bioavailability of lorlatinib oral solution was nearly complete compared with lorlatinib tablets.

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Conflicts of Interest

H.X. is a full-time employee and current stockholder at Pfizer Inc. M.T.O. is a full-time employee and may hold stock or stock options in Pfizer Inc. S.N. was an employee of Pfizer Inc. at the time this research was conducted and may hold stock or stock options in Pfizer Inc. L.P.J. was an employee of Pfizer Inc. at the time this research was conducted, and is a current stockholder at Pfizer Inc. He holds current employment with Bristol-Myers Squibb. K.G. is a full-time employee and current stockholder at Pfizer Inc. Y.K.P. is a full-time employee and current stockholder at Pfizer Inc.

Funding

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Data Accessibility Statement

On request and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply via a secure portal. To gain access, data requesters must enter into a data access agreement with Pfizer Inc.

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