Clinical Pharmacology
in Drug Development
2022, 11(1) 34–42

DOI: 10.1002/cpdd.1032

Evaluation of Proton Pump Inhibitor Esomeprazole on Crizotinib Pharmacokinetics in Healthy Participants

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Abstract

Crizotinib is a small-molecule, multitargeted tyrosine kinase inhibitor that exhibits decreased aqueous solubility at a higher pH. This open-label, randomized, phase 1 study (NCT01549574) evaluated the effect of multiple doses of the proton pump inhibitor esomeprazole on the pharmacokinetics (PK) of crizotinib and the safety of crizotinib with or without esomeprazole in healthy adults. Participants received a single 250-mg crizotinib dose after overnight fast or a single 250-mg crizotinib dose following esomeprazole 40 mg/day for 5 days. After a washout of ≥14 days, participants crossed over to the alternate treatment. Blood samples for plasma analysis were taken up to 144 hours after crizotinib dosing and relevant PK parameters estimated. Safety was assessed in all participants receiving ≥1 dose of study medication. Fifteen participants were evaluable for PK and safety for each treatment. Coadministration with esomeprazole resulted in a slight decrease (≈10%) in the crizotinib geometric mean area under the plasma concentration–time profile from time 0 to infinity (adjusted geometric mean ratio, 89.81% [90% confidence interval, 79.05-102.03]). Coadministration of esomeprazole did not affect peak crizotinib exposure. Adverse events (AEs) occurred in similar numbers between treatments; no serious or severe AEs occurred. The most common AE was diarrhea. Although esomeprazole decreased total exposure of crizotinib, it is not considered clinically meaningful, and dose modification is not required when crizotinib is coadministered with agents that affect gastric pH.

Keywords

crizotinib, esomeprazole, pharmacokinetics, proton pump inhibitor, tyrosine kinase inhibitor

Crizotinib is a competitive small-molecule inhibitor of the anaplastic lymphoma kinase (ALK), c-Met/hepatocyte growth factor receptor, c-ros oncogene 1 (ROS1), and Recepteur d'Origine Nantais (RON) receptor tyrosine kinases.[1–4] It is one of the first oncology drugs approved for a specific molecular-enriched patient population based on activity in that population.[5] As a first-in-class multitargeted tyrosine kinase inhibitor, crizotinib was initially approved for the treatment of patients with *ALK*-positive metastatic non–small cell lung cancer[5]; approvals were subsequently achieved for patients with *ROS1*-positive metastatic non–small cell lung cancer and pediatric patients with relapsed or refractory, systemic anaplastic large cell lymphoma that is *ALK* positive. Crizotinib is also being investigated for the treatment of other tumor types harboring *ALK* mutations.

In humans, crizotinib is primarily metabolized by cytochrome P450 (CYP) 3A with minor contribution from other CYP enzymes including CYP2C19.[6] A small amount of crizotinib is excreted in urine as the unchanged form.[7] As well as being a substrate, crizotinib is also a moderate inhibitor of CYP3A.[8] The mean apparent plasma terminal half-life of crizotinib 250 mg is 42 hours after a single dose,[9] and steady state is

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Submitted for publication 16 March 2021; accepted 13 September 2021.

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reached after 15 days with repeated administration.[8] The most abundant metabolite of crizotinib in plasma is its lactam metabolite, PF-06260182.[7] Metabolism of PF-06260182 is believed to be more dependent on CYP3A than crizotinib.[10] PF-06260182 is ≈2.5- to 7.7-fold less potent against ALK and 2.5- to 4-fold less potent against c-Met vs crizotinib.[7] To explore the potential effect of liver dysfunction on the pharmacokinetics (PK) of crizotinib, a clinical study was performed in patients with advanced cancer.[11] The results from this study suggested that the approved dose of 250 mg twice daily could be administered to patients with mild hepatic impairment, and reduced dose is necessary for patients with moderate hepatic impairment (200 mg twice daily) and severe hepatic impairment (250 mg once daily). A high-fat meal could result in a slight decrease in crizotinib exposure that was not considered clinically meaningful as the magnitude of change is within the variability of crizotinib PK.[12,13] Crizotinib demonstrates pH-dependent solubility in aqueous solution with decreased solubility at higher pH; solubility is >10 mg/mL at pH 1.6 and <0.1 mg/mL at pH 8.2.[14] Therefore, the coadministration of agents that can affect gastric pH may potentially affect crizotinib absorption.

Proton pump inhibitors (PPIs) are a group of drugs that have strong inhibitory effects on acid secretion in the stomach through suppression of the gastric proton pump (H,K-ATPase) and thus increasing gastric pH. Esomeprazole is the S-isomer (the active isomer) of the first approved PPI, omeprazole, and is indicated for the treatment of symptomatic gastroesophageal reflux disease, including healing and maintenance of erosive esophagitis and as part of a triple-drug regimen for *Helicobacter pylori* infection. Esomeprazole can maintain intragastric pH at a higher level and >4 for a longer period than other PPIs.[15,16] It has been demonstrated that the maximal effect of omeprazole and esomeprazole are reached after daily dosing for 5 days.[16]

The potential effect of esomeprazole on crizotinib PK was evaluated in the current study in healthy adult participants. The primary objective of the study was to evaluate the potential effect of multiple doses of esomeprazole on the PK of crizotinib and its lactam metabolite (PF-06260182).[7] The secondary objective of the current study was to assess the safety and tolerability of single crizotinib doses with or without esomeprazole in healthy adult participants.

Methods

The study protocol and informed consent documentation were reviewed and approved by the Ethics Committee of the Erasme Hospital (Brussels, Belgium) (NCT01549574). The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of study participants.

Participants

Participants were healthy men or women of non–childbearing potential, aged 18 to 55 years, with a body mass index of 17.5 to 30.5 kg/m^2 and a total body weight of >50 kg (110 lb). All participants signed an informed consent document before screening.

Exclusion criteria included evidence or history of clinically significant diseases, any condition possibly affecting drug absorption, a positive urine drug screen, history of excess alcohol consumption, treatment with an investigational drug within 30 days or 5 half-lives preceding the first dose of study medication, QT_c >450 milliseconds at screening, use of drugs or dietary supplements within 7 days or 5 half-lives (whichever was longer) before the start of study-drug treatment, blood donation of approximately ≥500 mL within 56 days before dosing, and a positive serology for hepatitis B or C.

Study Design

This study was a phase 1, open-label, randomized, 2-period, 2-sequence, cross-over, single-dose study in healthy adult participants to evaluate the potential effect of multiple doses of the PPI esomeprazole on the PK of crizotinib and to assess the safety and tolerability of single crizotinib doses with or without esomeprazole. This study was conducted at the Pfizer Clinical Research Unit (PCRU) at the Erasme Hospital, Brussels, Belgium.

The treatment sequences are shown in Table 1. Participants were given 1 of 2 treatments in period 1. Treatment A (the reference) was a single oral 250-mg dose of crizotinib after overnight fasting. Treatment B (the test treatment) was esomeprazole 40 mg per day orally for 5 days and a single 250-mg dose of crizotinib after overnight fasting on day 5 of esomeprazole treatment. After a washout period of at least 14 days, in period 2, participants received the alternate treatment to that received in period 1. A randomization number was allocated to each participant and retained throughout the study, and corresponded to a treatment schedule determined by a Pfizer-generated randomization code.

Participants were allowed to withdraw from the study at any time for the following reasons: at their own request; or at the discretion of the investigator or sponsor because of safety, behavioral reasons, or the inability of the participant to comply with the

Table 1. Treatment Sequences

Sequence	N	Period 1	Washout Period	Period 2
1	8	Treatment A (reference)	At least 14 days	Treatment B (test)
2	8	Treatment B (test)		Treatment A (reference)

Note: Treatment A (reference): single dose of crizotinib 250 mg after overnight fasting; Treatment B (test): esomeprazole 40 mg per day for 5 days and a single dose of crizotinib 250 mg after overnight fasting on day 5 of esomeprazole treatment.

protocol-required schedule of study visits or procedures. If the participant withdrew from the study and also withdrew consent for disclosure of future information, no further evaluations would have been performed and no additional data would have been collected. In treatment A, all participants were admitted to the PCRU on day 0, dosed with crizotinib 250 mg on day 1, discharged from the PCRU on day 5, and returned for an outpatient visit on day 7. In treatment B, all participants were admitted to the PCRU on day 0, dosed with esomeprazole 40 mg and discharged on day 1, continued esomeprazole 40 mg every day at home from day 2 to day 4, readmitted to PCRU and dosed with esomeprazole 40 mg and crizotinib 250 mg on day 5, discharged again on day 9, and returned for an outpatient visit on day 11. If necessary, a follow-up visit would be performed after the last period.

Crizotinib doses were given with 240 mL of ambient-temperature water and swallowed whole without chewing in the morning after overnight fasting. Esomeprazole doses were administered according to the label when given alone and under the same conditions as crizotinib when given with crizotinib. Crizotinib was supplied by Pfizer Inc as a commercial capsule, and esomeprazole was supplied at PCRU as a Nexium® 40-mg tablet. All study treatments at PCRU were administered under supervision. In order to standardize the conditions of PK sampling, restrictions were placed on eating, drinking, smoking, and physical activity before and/or during the study as previously described.[13]

Pharmacokinetic Sample Collection and Analytic Methods

Blood samples (3 mL) were collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid at time 0 (predose) and 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, and 144 hours after crizotinib dosing. Once collected, blood samples were processed immediately, and plasma concentrations of crizotinib and its metabolite, PF-06260182, were determined as previously described.[13]

Calibration standard responses were linear over the range of 0.200 to 200 ng/mL for crizotinib and PF-06260182.[13] Those samples with concentrations greater than the upper limit of quantification were diluted into calibration range. Concentrations below the lower limit of quantification (LLOQ, 0.200 ng/mL) were reported as below LLOQ.

The between-day assay accuracy, expressed as percent relative error, for quality-control (QC) concentrations ranged from –2.0% to –1.0% for crizotinib, and from 0.0% to 2.7% for PF-06260182 for the low (0.600 ng/mL), medium (70.0 ng/mL), high (150 ng/mL), and diluted (150 ng/mL) QC samples. Assay precision, expressed as the between-day percent coefficient of variation of the mean estimated concentrations of QC samples, was ≤4.3% for crizotinib and ≤4.6% for PF-06260182 for the low, medium, high, and diluted concentrations.

Pharmacokinetic Analysis

Plasma concentration–time data for crizotinib and PF-06260182 were analyzed to determine PK parameters using noncompartmental methods via electronic noncompartmental analysis (v2.2.3, Pfizer internal program, Groton, Connecticut).[13] The definition and method of determination for each PK parameter are listed in Table 2. Samples below the LLOQ were set to 0.00 ng/mL and actual sample collection times were used for analysis. Area under the plasma concentration–time profile (AUC) from time 0 extrapolated to infinity (AUC_{inf}) and plasma terminal elimination half-life ($t_{1/2}$) were reported where the following criteria were met: a well-characterized terminal phase defined as one with at least 3 data points, an r^2 ≥0.9 (goodness-of-fit statistics for the log-linear regression), and ≤20% extrapolation for AUC_{inf}.

Statistical Analysis

Sample-size calculation was based on estimates of within-subject deviations of 0.172 for $\log_e$ AUC_{inf} and 0.186 for $\log_e$ maximum plasma concentration (C_{max}) obtained from a previous PK study in healthy participants.

A sample size of 14 participants provided 90% confidence intervals (CIs) for the difference between treatments of ±0.1226 and ±0.1326 on the natural log scale for AUC_{inf} and C_{max}, respectively, with 90% coverage probability.

All treated participants with at least 1 crizotinib and one PF-06260182 concentration measurement were included in PK analysis. PK parameters were summarized

Table 2. Pharmacokinetic Parameter Determination

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration–time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear-log trapezoidal method
AUC_{inf}	Area under the plasma concentration–time profile from time 0 extrapolated to infinity	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} was the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{max}	Maximum plasma concentration	Observed directly from data
t_{max}	Time to C_{max}	Observed directly from data as time of first occurrence
$t_{1/2}$	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration–time curve; only those data points judged to describe the terminal log-linear decline were used in the regression
CL/F	Apparent clearance after oral dose	Dose/AUC_{inf} after oral dose
MRC_{max}	Metabolite to parent ratio of C_{max}	$(C_{max}/464.33)^a/(AUC_{last}/450.34)^b$
$MRAUC_{last}$	Metabolite to parent ratio of AUC_{last}	$(AUC_{last}/464.33)^a/(AUC_{last}/450.34)^b$
$MRAUC_{inf}$	Metabolite to parent ratio of AUC_{inf}	$(AUC_{inf}/464.33)^a/(AUC_{inf}/450.34)^b$

Pharmacokinetic parameter values were calculated using electronic noncompartmental analysis version 2.2.3.
[a] Metabolite (PF-06260182) data corrected for molecular weights (converted from ng to nmol).
[b] Crizotinib data corrected for molecular weights (converted from ng to nmol).

descriptively by treatment and analyte. Natural log-transformed exposure parameters (AUC and C_{max}) of crizotinib were analyzed as previously described.[13] The statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Adverse Events

All participants who received at least 1 dose of the study medication were included in the safety analyses.

Adverse events (AEs), electrocardiograms (ECGs), blood pressure, pulse rate, and safety laboratory data were reviewed on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, blood pressure, and pulse rate abnormalities of potential clinical concern were described. Safety data were summarized descriptively.

Results

A total of 16 male participants were enrolled and participated in the study between May 3 and May 29, 2012. One participant who was randomly assigned to sequence 1 (Table 1) was discontinued during period 1 due to the participant's decision to withdraw from the study for personal reasons. Another participant who was randomly assigned to sequence 2 discontinued before period 2 due to safety reasons (hematuria, which was considered moderate in severity and related to the study drug; the event resolved spontaneously ≈25 days later). A summary of demographic and baseline characteristics is shown in Table 3.

Table 3. Participant Demographics and Baseline Characteristics

	Participants (N = 16)
Male, %	100
Age category, y, n	
<18	0
18-25	0
26-35	5
36-45	7
>45	4
Mean age, y (range) [SD]	39.3 (26-53) [7.6]
Race, n	
White	14
Other	2
Mean weight, kg (range) [SD]	80.5 (61.8-102.8) [10.7]
Mean body mass index,[a] kg/m^2 (range) [SD]	24.9 (19.5-28.5) [2.4]
Mean height, cm (range) [SD]	179.8 (163-190) [6.5]

SD, standard deviation.
[a] Body mass index was defined as weight/(height × 0.01)^2.

In each treatment group, 15 participants were included in the PK analysis. Mean plasma concentration–time profiles of crizotinib and its metabolite PF-06260182 after each treatment are presented in Figure 1.

Crizotinib

Coadministration with esomeprazole (40 mg once daily × 5 days) decreased crizotinib total exposure (AUC_{inf})

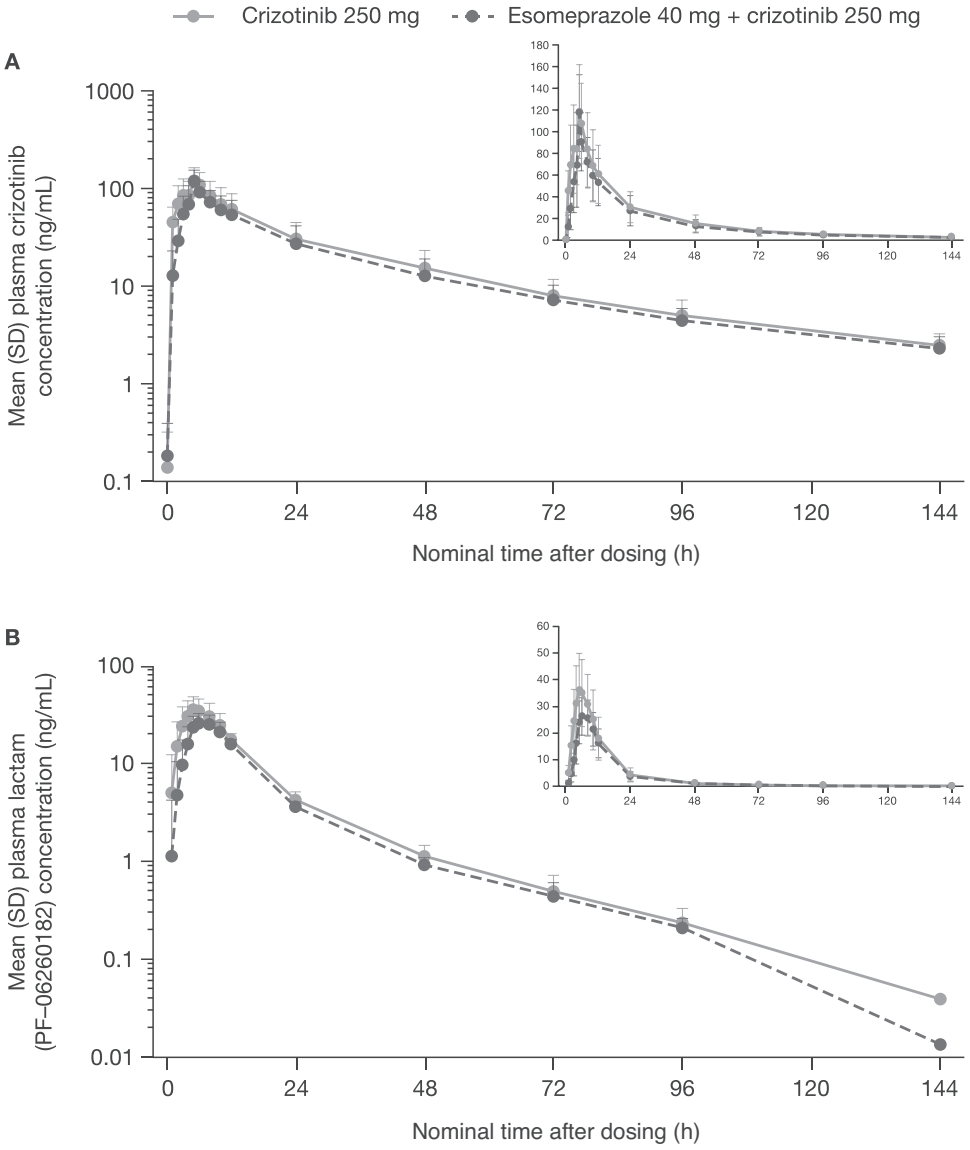

Figure 1. Mean (SD) plasma concentration–time curve of crizotinib (A) and PF-06260182 (B) on a semilogarithmic scale (the insets depict the same data on a linear scale). SD, standard deviation.

by ≈10% and had no effect on peak exposure (C_{max}) (Figures 2A and 2B). Median time to C_{max} values were 5 hours with or without esomeprazole (Table 4). No change in apparent $t_{1/2}$ was observed, with geometric mean values of 33.2 and 35.8 hours seen for crizotinib alone or with esomeprazole, respectively. Apparent oral clearance was similar for both treatments, with geometric mean values of 102.5 and 117.8 L/h for crizotinib alone or with esomeprazole, respectively.

The ratios of adjusted geometric means (90%CI) of crizotinib AUC_{inf} and C_{max} were 89.81% (79.05-102.03) and 101.84% (91.51-113.33), respectively, following administration of crizotinib 250 mg + esomeprazole (40 mg once daily × 5 days) relative to crizotinib 250 mg (Table 5). The corresponding 90%CI for the adjusted geometric means for AUC_{inf} fell marginally outside of the lower (80%) limit for bioequivalence, whereas the corresponding 90%CIs for the adjusted geometric mean for the C_{max} ratios were contained within the 80% to 125% bioequivalence range.

PF-06260182

Esomeprazole treatment (40 mg once daily for 5 days) resulted in moderate decreases of approximately 18% and 23% in PF-06260182 AUC_{inf} and C_{max}, respectively (Figures 2C and 2D). Median time to C_{max} values were similar with or without esomeprazole, with a range of 5 to 6 hours (Table 4). No change in apparent $t_{1/2}$ was

Table 4. Summary of Plasma Crizotinib and PF-06260182 Pharmacokinetic Parameter Values Following Single Oral Crizotinib Doses Alone and After 5 Days of Daily Esomeprazole 40 mg Dosing

	Parameter Summary Statistics[a] by Treatment			
	Crizotinib 250 mg (n = 15)		Esomeprazole 40 mg + Crizotinib 250 mg (n = 15)	
Parameter[b] (Units)	Geometric Mean (%CV)	Arithmetic Mean ± SD	Geometric Mean (%CV)	Arithmetic Mean ± SD
Crizotinib				
AUC_{inf}, ng • h/mL	2438 (42)	2623 ± 1091	2122 (39)	2265 ± 891
AUC_{last}, ng • h/mL	2307 (43)	2490 ± 1072	2022 (40)	2166 ± 876
CL/F, L/h	102.5 (38)	109.9 ± 42.2	117.8 (33)	124.8 ± 40.9
C_{max}, ng/mL	118.5 (31)	124.5 ± 39.2	114.8 (28)	119.0 ± 32.9
t_{max}, h	5.00 (2.00-6.00)		5.00 (3.00-6.00)	
$t_{1/2}$, h		33.2 ± 7.0		35.8 ± 4.4
PF-06260182[c]				
AUC_{inf}, ng • h/mL	451 (47)	492 ± 232	364 (33)	383 ± 127
AUC_{last}, ng • h/mL	451 (46)	490 ± 225	357 (34)	376 ± 126
C_{max}, ng/mL	35.9 (34)	37.9 ± 13.0	26.8 (25)	27.7 ± 6.8
t_{max}, h	5.02 (5.00-8.00)		6.00 (5.00-8.05)	
$t_{1/2}$, h		19.7 ± 7.1		19.5 ± 5.9
$MRAUC_{last}$	0.19 (18)		0.17 (13)	
$MRAUC_{inf}$	0.18 (16)		0.17 (12)	
MRC_{max}	0.29 (26)		0.23 (17)	

AUC_{inf}, area under the plasma concentration–time profile from time 0 extrapolated to infinity; AUC_{last}, area under the plasma concentration–time profile from time 0 to the time of the last quantifiable concentration; CL/F, apparent clearance after oral dose; C_{max}, maximum plasma concentration; CV, coefficient of variation; $MRAUC_{inf}$, metabolite to parent ratio of AUC_{inf}; $MRAUC_{last}$, metabolite to parent ratio of AUC_{last}; MRC_{max}, metabolite to parent ratio of C_{max}; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; t_{max}, time to C_{max}.
[a] Geometric mean (%CV) and arithmetic mean ± SD for all except: median (range) for t_{max} and arithmetic mean ± SD only for $t_{1/2}$.
[b] Pharmacokinetic parameters are defined in Table 2.
[c] n = 14 for AUC_{inf}, $t_{1/2}$, and $MRAUC_{inf}$ of PF-06260182 in the crizotinib 250-mg group.

Table 5. Statistical Summary of Treatment Comparisons for Crizotinib and PF-06260182 With or Without PPI

	Adjusted Geometric Means			
Parameter[a] (Units)	Test[b]	Reference[b]	Ratio (%) (Test/Reference)	90%CI (%)
Crizotinib				
AUC_{inf}, ng • h/mL	2125	2366	89.81	79.05-102.03
AUC_{last}, ng • h/mL	2014	2238	89.99	78.84-102.71
C_{max}, ng/mL	116.8	114.7	101.84	91.51-113.33
PF-06260182				
AUC_{inf}, ng • h/mL	367.8	446.0	82.46	71.13-95.60
AUC_{last}, ng • h/mL	359.8	436.9	82.34	71.08-95.39
C_{max}, ng/mL	26.9	34.8	77.38	69.12-86.62

AUC_{inf}, area under the plasma concentration–time profile from time 0 extrapolated to infinity; AUC_{last}, area under the plasma concentration–time profile from time 0 to the time of the last quantifiable concentration; C_{max}, maximum plasma concentration; PPI, proton pump inhibitor.
[a] Pharmacokinetic parameters are defined in Table 2.
[b] Test: esomeprazole 40 mg per day for 5 days and single 250-mg crizotinib dose after overnight fasting on day 5 of esomeprazole treatment; reference: single 250-mg crizotinib dose after overnight fasting.

observed, with a mean value of ≈20 hours for both treatments.

The ratios of adjusted geometric means (90%CI) of PF-06260182 AUC_{inf} and C_{max} were 82.46% (71.13-95.60) and 77.38% (69.12-86.62), respectively, following administration of crizotinib 250 mg + esomeprazole (40 mg once daily × 5 days) relative to crizotinib 250 mg (Table 5). This change in exposure is still within the PK variability of ≈30% to 40%.

Modest decreases in metabolite (PF-06260182) to parent (crizotinib) ratios for measures of systemic exposure (C_{max} and AUC) were observed following administration of crizotinib with esomeprazole compared with crizotinib alone (Table 4).

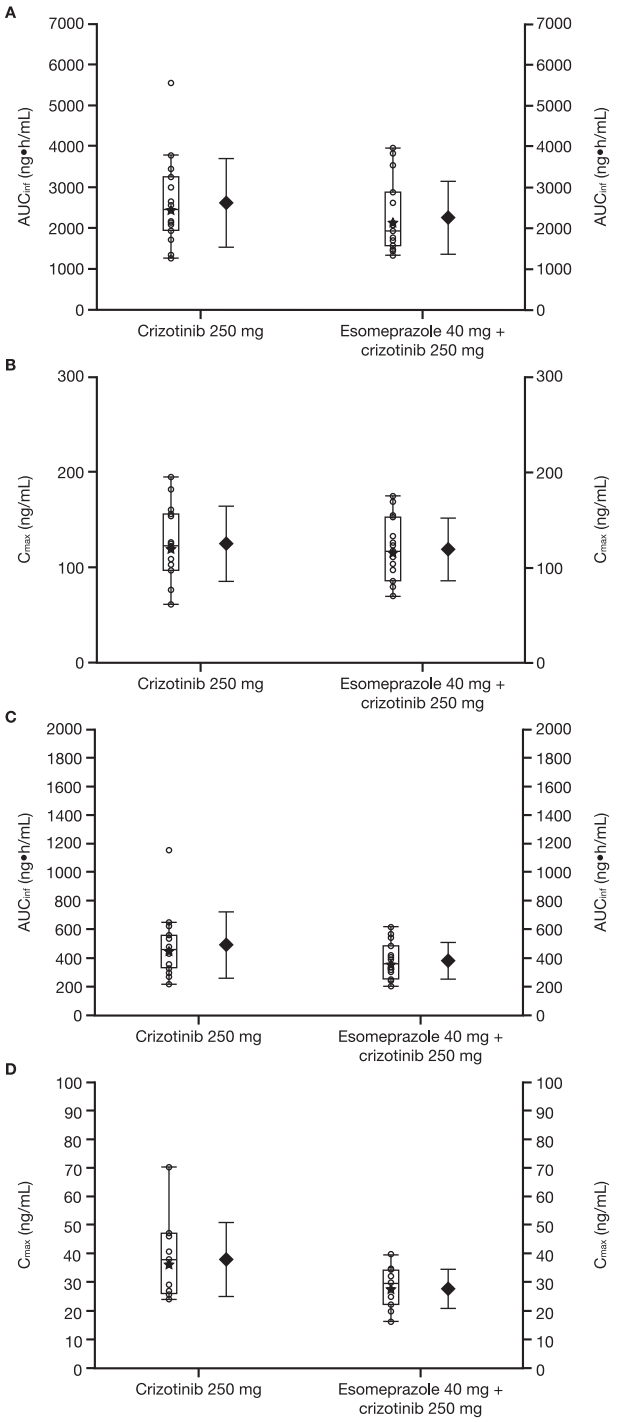

Figure 2. Individual and mean AUC_{inf} and C_{max} values by treatment. (A) Crizotinib AUC_{inf}; (B) crizotinib C_{max}; (C) PF-06260182 AUC_{inf}; (D) PF-06260182 C_{max}. Circles represent the individual values and stars represent geometric means. Box plots provide median and 25%/75% quartiles with whiskers to the last point within 1.5 times the interquartile range. Arithmetic means (diamonds) and standard deviations are shown to the right of the box plots. AUC_{inf}, area under the plasma concentration–time profile from time 0 extrapolated to infinity; C_{max}, maximum plasma concentration.

Safety and Tolerability

A summary of the incidence of treatment-emergent and treatment-related AEs is provided in Table 6. The most frequently reported AE in this study was diarrhea, which was mild in severity, treatment related, and experienced by 11 participants during treatment with crizotinib 250 mg and by 7 participants during the combined treatment of multiple doses of esomeprazole followed by a single dose of crizotinib. The only other AE that occurred in >2 participants during any treatment phase was abdominal pain, which was experienced by 3 participants during treatment with crizotinib 250 mg and was considered treatment related. By system organ class, gastrointestinal disorders (crizotinib 250 mg, 11 participants; esomeprazole 40 mg, 3 participants; esomeprazole 40 mg + crizotinib 250 mg, 10 participants) and nervous system disorders (crizotinib 250 mg, 4 participants; esomeprazole 40 mg, 2 participants; esomeprazole 40 mg + crizotinib 250 mg, 1 participant) were the most common disorders.

Twenty-four of 28 AEs during treatment with crizotinib 250 mg, 7 of 9 AEs during treatment with esomeprazole 40 mg, and 17 of 23 AEs during combined treatment of esomeprazole followed by crizotinib were considered related to study treatment. The only treatment-related AEs that were reported in >2 participants during any of the treatments were diarrhea (crizotinib 250 mg, 11 participants; esomeprazole 40 mg + crizotinib 250 mg, 7 participants) and abdominal pain (crizotinib 250 mg, 3 participants). By system organ class, treatment-related gastrointestinal disorders (crizotinib 250 mg, 11 participants; esomeprazole 40 mg, 3 participants; esomeprazole 40 mg + crizotinib 250 mg, 9 participants) were the most common disorders.

Discussion

The modest decrease in crizotinib overall systemic exposure seen with esomeprazole treatment is not unexpected considering the effect of a PPI on gastric pH and pH-dependent solubility of crizotinib. Since crizotinib's solubility is higher at lower pH values (>10 mg/mL at pH 1.6 and 0.1 mg/mL at pH 7.7), an increase in gastric pH could theoretically affect the speed and extent of drug absorption. The crizotinib lactam metabolite PF-06260182 also demonstrated reduced systemic exposure with esomeprazole coadministration. Since esomeprazole is a reversible inhibitor of CYP2C19,[17] and CYP2C19 has a minor contribution to crizotinib metabolism,[6] the effect of esomeprazole on crizotinib exposure is slightly offset and a relatively bigger change in exposure was observed for metabolite PF-06260182 compared with crizotinib. Overall, the extent of the changes in systemic exposure of both

Table 6. Summary of Treatment-Emergent Adverse Events

	Number of All Causality AEs (Number of Treatment-Related AEs)	
	Crizotinib 250 mg (N = 15)	Esomeprazole 40 mg + Crizotinib 250 mg (N = 15)
Participants evaluable for AEs	15	15
Number of AEs	28 (24)	23 (17)
Participants with AEs	12 (12)	13 (10)
Participants with serious AEs	0	0
Participants with severe AEs	0	0
Discontinuations due to AEs	0	1 (1)
Dose reductions or temporary discontinuation due to AEs	0	0
AEs in >1 participant in either group, by MedDRA preferred term		
Diarrhea	11 (11)	7 (7)
Abdominal pain	3 (3)	0
Abdominal pain upper	0	2 (2)
Abnormal gastrointestinal sounds	1 (1)	2 (2)
Fatigue	2 (2)	1 (1)
Nausea	2 (2)	1 (1)
Dizziness	2 (2)	0
Headache	2 (2)	0

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities (version 15.0).

crizotinib and PF-06260182 with PPI treatment are not considered clinically meaningful, as the magnitude of change in exposure (10%) is well within the variability of crizotinib PK (≈30%-40%), and do not indicate the need for crizotinib dose modification when administered with agents that affect the gastric pH, such as PPIs and H_2-receptor antagonists.

A single 250-mg dose of crizotinib was generally safe and well tolerated. The most common AE was diarrhea, which was mild in severity. There were 2 permanent discontinuations, one of which was due to a treatment-related AE, hematuria, which was moderate in severity and resolved spontaneously. There were no severe AEs, serious AEs, or deaths during this study. There were no laboratory abnormalities, vital sign measurements, or ECG measurements that were considered to be clinically meaningful.

Conclusion

The findings from this study indicate that crizotinib can be coadministered with acid-reducing agents, such as PPIs, without dose adjustment.

Acknowledgments

The authors would like to thank the study participants and their operational colleagues who contributed to the execution of the study.

Conflicts of Interest

All authors are employees or former employees of Pfizer and may own stock or stock options in Pfizer. Editorial support was provided by Annette Smith, PhD, of CMC AFFINITY, McCann Health Medical Communications, and Kate Silverthorne, PhD, on behalf of CMC AFFINITY, and was funded by Pfizer.

Data-Sharing Statement

Upon 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 Inc will provide access to individual deidentified 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 deidentified 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 requestors must enter into a data access agreement with Pfizer.

Funding

This study was sponsored by Pfizer Inc.

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