INTRODUCTION

Oncogenic fusions of anaplastic lymphoma kinase (ALK) are present in ~ 5% of patients with non-small cell lung cancer (NSCLC).\(^1\,^2\) Targeted receptor tyrosine kinase inhibitor (TKI) treatment is effective in this population\(^3\); however, acquired resistance to first and second generation ALK inhibitors is common.\(^4\) Lorlatinib is a third generation, adenine triphosphate (ATP)-competitive inhibitor of ALK, indicated for the treatment of patients with ALK-positive NSCLC following prior ALK inhibitor therapy.\(^5\) It is active across a range of ALK mutations, including those associated
with acquired resistance to first and second generation ALK inhibitors.\(^6\)

The lorlatinib first-in-patient phase I/II dose escalation and expansion study B7461001 (NCT01970865) enrolled patients with advanced ALK-positive or c-ROS oncogene 1 (ROS1)-positive NSCLC, with or without asymptomatic central nervous system (CNS) metastases.\(^7\) Based on safety, efficacy, and clinical pharmacology data from the phase I portion of the study, 100 mg once daily (q.d.) lorlatinib was selected as the recommended phase II dose.\(^7\) The efficacy of 100 mg q.d. lorlatinib was established in the phase II portion of the study and was the basis of regulatory approval.\(^8,9\)

In the phase I portion of B7461001, the accumulation after multiple dosing was less than expected based on the plasma half-life, suggesting that lorlatinib undergoes metabolic auto-induction. Lorlatinib is metabolized primarily by cytochrome P450 (CYP)3A and UGT1A4, and to a lesser extent by CYP2C8, CYP2C19, CYP3A5, and UGT1A3.\(^10\)

In the phase I portion of B7461001, levels of CYP3A4 activity initially increased with time following multiple dosing, as measured by urine 6-beta-hydroxy-cortisol/cortisol and plasma 4-beta-hydroxy-cholesterol/cholesterol ratios, but then gradually reached a plateau. Together, these observations support time-dependent auto-induction in lorlatinib clearance. Additional information on lorlatinib pharmacokinetics (PK) came from an open-label crossover drug interaction study (B7461008) in healthy volunteers, which indicated that co-administration of the proton-pump inhibitor (PPI) rabeprazole reduced lorlatinib maximum concentration (C\(_{\text{max}}\)) by ~ 30\% but had no effect on lorlatinib area under the curve to infinity (AUC\(_{\text{inf}}\)). Furthermore, administration of lorlatinib with a high-fat meal was found not to have a meaningful effect on lorlatinib exposure.\(^11\)

Here, we describe the development of a population PK (PopPK) model characterizing lorlatinib plasma PK based on data from the phase I/II clinical study and six studies in healthy participants. The potential effects of various covariates were assessed, including demographic factors, CYP metabolizer phenotype, measures of hepatic and renal function, formulation, PPI, and food effect.

**METHODS**

**Analysis dataset**

Data were pooled from patients with advanced ALK-positive or ROS1-positive NSCLC enrolled in Study B7461001, and from healthy subjects enrolled in six phase I studies in healthy participants (Table 1). In Study B7461001, serial PK sampling was conducted following single dosing, and after 15 days of continuous dosing (cycle 1, day 15; patients only); sparse sampling was performed in a limited number of patients after 8 days of continuous dosing (cycle 1, day 8) and on day 1 of cycles 2–5. Primary efficacy and safety data from Study B7461001 have been previously published.\(^7,9\)

All trials were conducted in accordance with Good Clinical Practice Guidelines and the ethical principles that have their origin in the Declaration of Helsinki, and all patients provided written informed consent.

**Modeling: Software and strategy**

The analysis was performed using nonlinear mixed effects modeling methodology as implemented in NONMEM version 7.3 (ICON, Dublin, Ireland) using the first order conditional estimation method with interaction (FOCEI). Inspection of
## Table 1
Summary of study populations included in the PopPK analysis

| Study design | Lorlatinib dosing regimen | Number of subjects included in PopPK analysis | Time points of PK sampling |
|--------------|----------------------------|----------------------------------------------|---------------------------|
| B7461001 (NCT01970865) Phase I/II open-label multicenter, multiple dose escalation/expansion study in patients with advanced ALK+ or ROS1+ NSCLC | Phase I: 10, 25, 50, 75, 100, 150, 200 mg orally q.d., or 35, 75, or 100 mg orally b.i.d. | 54 | Day −7: predose, 0.5, 1, 2, 3, 4, 6, 8, 9, 24, 48, 72, 96, and 120 h postdose. Cycle 1 day 1 and cycle 1 day 8: predose, 1 and 4 h postdose. Cycle 1 day 15: predose, 0.5, 1, 2, 3, 4, 6, 8, 9, and 24 h (24-h sample not required for b.i.d. dosing). Day 1 of cycles 2–5: predose and 1 h postdose |
| B7461004 (NCT03184168) Open-label, single dose, single center mass balance study in healthy male participants | Single oral 100 mg dose | 6 | Full PK: Day −7: predose, 0.5, 1, 2, 3, 4, 6, 8, 9, 24, 48, 72, 96, and 120 h postdose. Cycle 1 day 1 and cycle 1 day 8: predose, 1, 2, and 4 h postdose. Cycle 1 day 15: predose, 0.5, 1, 2, 3, 4, 6, 8, 9, and 24 h. Day 1 of cycles 2–5: predose, 1 and 2 h postdose. Day 1 of cycle 6 and day 1 of every other cycle thereafter: predose Sparse PK: predose on day 1 of cycles 1–5 and predose on cycle 7 day 1, cycle 8 day 1, and cycle 10 day 1 |
| B7461005 Phase I, randomized open-label crossover study to assess relative bioavailability in healthy participants | Lorlatinib 100 mg tablets | 20 | Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 10 h postdose |
| B7461007 Phase I, single dose, randomized, open-label, two-period, two-treatment, two-sequence, crossover study of lorlatinib in healthy participants to assess absolute bioavailability | Treatment A: 50 mg i.v. Treatment B: 100 mg oral tablet | 11 | Predose, 0.5, 1, 1.5, 2, 4, 6, 12, 24, 48, 72, 96, 120, and 144 h postdose |
| B7461008 (NCT02569554) Phase I randomized crossover, open-label, 4-period study in healthy participants to evaluate effect of rabeprazole and food on lorlatinib PK and to assess bioavailability of oral solution vs. tablet formation | Single oral dose: 100 mg | 26 | Predose, 0.5, 1, 1.5, 2, 4, 6, 12, 24, 48, 72, and 96 h postdose |
| B7461011 Phase I, open-label, two-period, two-treatment, fixed sequence, crossover study to estimate the effect of multiple dose rifampin on the single dose PK of lorlatinib in healthy participants | Single oral dose: 100 mg | 12 | Predose, 0.5, 1, 1.5, 2, 4, 6, 12, 24, 36, 48, 60, 72, 96, and 120 h postdose |
| B7461016 Phase I, randomized, single dose, open-label, study to assess lorlatinib bioequivalence in healthy participants under fasted conditions | Single oral dose: 100 mg | 20 | Predose, 0.5, 1, 1.5, 2, 4, 6, 12, 24, 36, 48, 60, 72, 96, and 120 h postdose |

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; PopPK, population pharmacokinetic; ROS1, c-ROS oncogene.

Potential covariates were screened using visual examination of diagnostic plots and generalized additive modeling (GAM), then underwent stepwise covariate model (SCM) building to obtain a stable final model, including covariates that significantly improved the adequacy of the model. SCM was implemented using Perl-speaks-NONMEM (PsN) 4.2.0.
followed by a separate NONMEM run, including covariance estimation.

Additional graphical and statistical analysis was done with R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Lorlatinib clearance estimation

As PK data corresponded to samples collected after single dose administration, or at steady-state following auto-induction, lorlatinib clearance (CL) was estimated using an initial clearance after single dosing (CLI), and subsequently a time-varying clearance that achieves its maximum value at steady-state (CLMX) according to the following expression:

\[
CL = \begin{cases} 
  CLI & \text{if Single Dose} \\
  CLMX \times (1 - e^{-\text{IND} \times t}) & \text{if Multiple Doses}
\end{cases}
\]

Where IND is the induction rate constant and \(t\) is time postdose.

Random effects model development

Between-subject variability for CL, volume of distribution of the central compartment (\(V_2\)), volume of distribution of the peripheral compartment (\(V_3\)), inter-compartmental clearance (\(Q\)), first order absorption rate constant (\(k_a\)), and bioavailability (\(F\)) were modeled using multiplicative exponential random effects of the form:

\[
\theta_i = \theta \times e^{\omega_i}
\]

where \(\theta\) is the typical individual (population mean) parameter value and \(\theta_i\) denotes the between-subject random effect accounting for the \(i^{th}\) patient’s deviation from the typical value having zero mean and variance \(\omega^2\). The approximate percent coefficient of variation (%CV) was reported as:

\[
\% CV = \sqrt{\omega^2} \times 100\%
\]

The multivariate vector of between-subject random effects has a variance-covariance (\(\Omega\)) matrix. The base structural model was developed using a diagonal \(\Omega\) matrix first and a full block (unstructured) \(\omega\) was explored before and after covariates were included. The most stable \(\Omega\) structure with successful $COV estimates was selected for the base model.

Residual variability was initially modeled using the combined additive and proportional error model. Simplifications of this model were explored (e.g., proportional error only) when estimates of additive error were small.

Inclusion of covariates and full model development

The covariates assessed in the PopPK analysis are shown in Table 2. These were selected based on scientific rationale and clinical interest. As lorlatinib is metabolized extensively in the liver, metabolizer phenotypes for CYP3A5 and CYP2C19, and baseline bilirubin, baseline alanine aminotransferase (ALT), and baseline hepatic function were investigated as covariates on clearance. As severe renal impairment can also influence the PK of drugs metabolized in the liver, and chronic renal failure can reduce CYP activity, the impact of renal impairment was assessed by the inclusion of baseline standardized creatinine clearance (WNCL) as a covariate on \(V_2\), \(CL\), and \(F\). To confirm previously reported findings on the impact of PPI use and food effect on lorlatinib PK, PPI use and food effect were investigated as covariates on \(k_a\) and \(F\).

These covariates were subsequently tested for significance in a stepwise manner using the SCM application in PsN with statistical significance criterion of \(\alpha = 0.05\) for the forward inclusion step, which corresponded to a change in objective function value (\(\Delta OFV\)) of 3.84 based on \(\chi^2\) with degrees of freedom (df) = 1. The full model was then subjected to a backward elimination step with a statistical significance criterion of \(\alpha = 0.01\), which corresponded to a \(\Delta OFV\) of 6.65 based on \(\chi^2\) with df = 1.

Categorical covariates were included using a linear function. The covariate parameter structures for continuous covariates (linear and power functions) were tested for all the included covariates in parallel whenever a new covariate was incorporated and was determined based on OFV.

In addition to \(\Delta OFV\), the final model was selected after careful review of \(\omega\) and \(\sigma\) values. Furthermore, prediction-based, residual-based, and simulation-based diagnostics were considered for covariate inclusion in the final model. Empirical Bayes estimate-based diagnostics were not used due to high parameter shrinkage.

Derivation of standardized creatinine clearance

Baseline creatinine clearance (BCCL) was determined using the Cockcroft-Gault equation.14 Because allometric weight scaling was used \(a\ priori\) on the base model, CL, \(V_2\), and BCCL all had a dependence on baseline body weight (BWT); to properly assess the relation between BCCL and CL, BCCL was transformed to WNCL as follows15:
TABLE 2  Evaluated covariates

| PK parameters | Covariates |
|---------------|------------|
| CL            | AGE, SEX, PTST, CYP2C19, CYP3A5, CYP2C9, TDOSE, RACE, BALB, BALK, BBIL, BTG, BHGRADE, BRGRADE, WNCL, BALT |
| V2            | AGE, SEX, BRGRADE, BTG, RACE, WNCL |
| k<sub>a</sub>  | FOOD, PSCI, PPI |
| F             | FOOD, PSCI, PPI, TDOSE, BHGRADE, BRGRADE, WNCL, BALT, CYP2C19, CYP3A5, CYP2C9 |

WNCL<sub>i</sub> = BCCL<sub>i</sub> × \( \frac{72}{\text{BWT}_i} \)

Final model development

To obtain the most parsimonious and stable final model, the candidate covariate model resulting from the backward elimination step in SCM was subjected to a separate NONMEM run, including covariance estimation excluded in PsN when running SCM. Signs of model overparameterization and poorly estimated parameters were examined.

Outliers

Outliers were identified in both the base and final models using the absolute value of conditional weighted residuals (CWRES) and individual weighted residuals (IWRES) following the criteria |CWRES|>6 and |IWRES|>6. The influence of the set of outliers was evaluated by comparing estimates of the key PK parameters (i.e., the structural and covariate fixed effects on CL), with and without the outliers removed. In addition to outliers identified by CWRES or IWRES, inspection of the dataset for illogical values (e.g., very high predose concentrations, or very low concentrations noted near typical time to maximum concentration \( [T_{\text{max}}] \)) was performed.

Assessment of model adequacy and predictive performance

At all stages of model development (base and final), assessment of model adequacy was conducted through multiple approaches, including ΔOFV, visual inspection of different diagnostic plots, precision of the parameter estimates, as well as decreases in both between-subject variability and residual variability.

A battery of diagnostic testing was conducted to evaluate the goodness of fit and detect any violation of assumptions. Plots of observed concentrations (OBS) versus population predictions (PRED) and OBS versus individual predictions (IPRED) were evaluated for randomness around the line of unity. Evaluation was also performed on longitudinal profiles of PK concentration to compare observations and predictions. Plots of CWRES versus time and IWRES versus time were evaluated for randomness around the zero line. For parameters with reasonable empirical Bayes estimate for interindividual variability (ETA) shrinkage, distribution of ETAs was checked to ensure normal distribution. In addition, plots of ETAs versus covariate for parameters with reasonable ETA shrinkage in the final model were compared with similar plots for the base model to demonstrate that the final model accounted for trends observed with the base model. Relative standard error (RSE) of the parameter estimates were generated based on asymptotic standard errors generated from the NONMEM covariance step. The 95% confidence interval (CI) around the parameters was generated from bootstrap estimates from 1,000 resampled datasets.

A comparison of the OFV statistics and parameter estimates for the base and final models were used to assess the degree of parsimony of the final model, and parameter magnitude was used to determine the clinical relevance of the covariate effects. A comparison of \( \omega^2 \) between the models was made to assess the reduction in variance by inclusion of covariate effects. ETA shrinkage estimated as \( (1-\text{Stdev}(\eta\text{EBE})/\omega) \) was also evaluated.

The performance of the final model was evaluated by simulating data using the parameter estimates from the final model (fixed and random effects) and by conducting a prediction-corrected visual predictive check (pcVPC), which normalizes observed and simulated dependent variables based on the typical population to remove variability associated with binning across independent variables. Simulations were performed using patient status variable (PTST) as well
as the dosing and sampling history from the original data-
set. From these simulations, concentration-time data were
summarized using median, low, and high percentiles. The
concordance between individual observations and simulated
values as well as the distribution of observed and simulated
data were evaluated.

Sensitivity analysis of covariate effects on exposure
A clinically meaningful change in lorlatinib plasma expo-
sure was considered as one that would necessitate lorlat-
inib dose adjustment. Based on observations from the dose
escalation portion of Study B7461001, a clinical no-effect
boundary of 70–142.9% (equivalent to a 30% change on the
log scale) was defined for lorlatinib exposure, as compared
with 100 mg q.d.

In order to assess whether the effect of the covari-
ates included in the final model resulted in a meaningful
change in lorlatinib plasma exposure warranting a dose
adjustment, 500 individuals were simulated from the
final model parameters for each of the covariates, at var-
ious extremes, and compared with the simulations for a
typical individual; defined as a 70 kg individual with no
PPI use, WNCL of 100 mL/min, baseline albumin (BALB)
of 4 mg/dL, and dosed at 100 mg with steady-state C_{\text{max}}
of 606 ng/mL and a steady-state AUC_{\text{lag}} of 5180 ng.h/
ml. Forest plots were constructed using the conditions
reported on the Y-axis as fixed effects and the simulations
as random effects.

RESULTS

Analysis dataset
The final analysis dataset was composed of data from 425
study participants, including 330 patients with advanced
ALK-positive or ROS1-positive NSCLC and 95 healthy par-
ticipants (Table 1). Baseline covariate data from the PopPK
analysis set are summarized in Table 3.

Model development
Lorlatinib PK was initially described using a one-compart-
ment model defined in terms of CL, V, k_{a}, and F; however,
addition of a second compartment significantly improved
model fit. The initial base model failed to adequately char-
acterize C_{\text{max}} in many of the subject PK profiles; therefore,
a sequential zero-order and first-order (k_{a}) absorption (with
D_{1} parameter) was investigated. Allometric BWT correction
was included a priori in the base model on CL and V_{2} by
using a scaling factor exponent of 0.75 and 1, respectively,
to remove a confounding effect observed between BWT and
sex. A final two-compartment base model, with auto-induc-
tion of CL, and sequential zero-first order absorption, defined
in terms of CL, V_{2}, V_{3}, Q, zero-order input duration (D_{1}), k_{a},
and F was found to best describe the data and was carried
forward to the next stage of modeling.

Of the evaluated covariates, BALB, WNCL, and lorlatinib
total daily dose (TDOSE) were found to be significant and
were retained as covariates on CL in the final model. PPI use
was retained as a covariate on k_{a}.

The final PopPK model parameters are shown in Table 4.
Lorlatinib CL, V_{2}, and k_{a} for a typical subject were parame-
terized as follows:

\[
CL = \begin{cases} 
9.04 \text{ (L/h)} \times \left( \frac{\text{BWT}}{70} \right)^{0.75} \times \left(1 + 0.00138 \times (\text{TDOSE} - 100)\right) \\
\times \left(1 + 0.0668 \times (\text{BALB} - 4.00)\right) \times \left( \frac{\text{WNCL}}{100} \right)^{0.235} \text{ if Single Dose} \\
14.5 \text{ (L/h)} \times (1 - e^{-0.01999 \times \text{PPI}}) \times \left( \frac{\text{BWT}}{70} \right)^{0.75} \times \left(1 + 0.00138 \times (\text{TDOSE} - 100)\right) \\
\times \left(1 + 0.0668 \times (\text{BALB} - 4.00)\right) \times \left( \frac{\text{WNCL}}{100} \right)^{0.235} \text{ if Multiple Doses}
\end{cases}
\]

V_{2} = 121 \text{ (L)} \times \left( \frac{\text{BWT}}{70} \right).

\[k_{a} = 3.11 \text{ (h}^{-1} \text{)} \times (1 - 0.675 \times \text{PPI}).\]

Lorlatinib CL was estimated to be 9.04 L/h, and CLMX
was estimated to be 14.5 L/h. IND was estimated to be
0.0199 h^{-1}, or 0.478 days^{-1}, corresponding to an induction
half-life of ~ 34.8 hours (1.45 days). This suggests that lor-
atinib initial clearance will approach CLMX after 7.25 days,
assuming that the metabolic auto-induction of lorlatinib
reaches steady-state in ~ 5 half-lives. Thus, the exposure at
cycle 1, day 15 represents the lorlatinib exposure after the
completion of auto-induction. The typical value for V_{2} was
estimated to be 121 L. For the sequential zero-first order
absorption, D_{1} was estimated to be 1.15 hours and the typ-
ical value for k_{a} was estimated to be 3.11 (h^{-1}). The PPI use
covariate was equal to 1 if the subject was randomized to receive PPI with lorlatinib and 0 otherwise. In addition, \( V_3 \) was estimated to be 155 L, \( Q \) was estimated to be 22.0 L/h, and \( F \) was estimated to be 0.759.

Plots of observed concentrations versus PRED and IPRED are presented in Figure 1. Several data points were identified as potential outliers; however, after exclusion of these data points, the parameter estimates did not change by greater than 10%. This suggested that the outliers were not influential, and they were therefore retained in the final dataset.

As shrinkage was relatively high (>30%) for all parameters except \( CL \) and \( F \), ETA plots were considered unreliable and are not presented.

**Final model predictive performance**

The pcVPC plots showed that the final model had good predictive performance, with the 5th, 50th, and 95th percentiles of the observed data lying within the 90% CIs of the simulated 5th, 50th, and 95th percentiles (Figure 2).

**Covariate effects on lorlatinib steady-state exposure**

A sensitivity analysis was conducted to assess whether the covariates included in the final model affected lorlatinib exposure to an extent that may warrant dose adjustment.

In the final PopPK model, an individual with low BWT (50 kg; 10th percentile of the analysis population) was predicted to have a 22.3% reduction in \( CL \) and 28.6% reduction in \( V_2 \) relative to a typical patient. For an individual with high BWT (91.3 kg; 90th percentile), \( CL \) and \( V_2 \) were increased 22% and 30.4%, respectively, relative to the typical patient.

According to the final PopPK model, individuals with low BALB (3.2 mg/dL; 10th percentile) had a 5.3% reduction in \( CL \), whereas individuals with high BALB (4.6 mg/dL; 90th percentile) had a 4% increase in \( CL \) compared with the typical patient (BALB 4 mg/dL).

Individuals with PPI use had a 67.5% decrease in \( k_a \) relative to a typical patient without PPI use. This change in absorption rate constant did not impact meaningfully on overall lorlatinib exposure (represented by \( C_{max} \) and \( AUC \)) as shown in Figure 3.

TDOSE was also found to be a significant predictor of \( CL \). Individuals who received 10 mg q.d. lorlatinib had a 12.4% lower \( CL \) (both initial and time-varying induced \( CL \)) compared with individuals receiving 100 mg q.d. lorlatinib. At the lowest possible lorlatinib exposure at 100 mg q.d. (based on an individual with BWT of 50 kg, BALB of 4.6 mg/dL and PPI use), the final PopPK model predicted an increase in \( CL \) of 26.9%, an increase in \( V_2 \) of 30.4%, and a decrease in \( k_a \) of 67.5%, compared with a typical patient.

**TABLE 3** Summary of baseline covariates

| Covariate | PopPK analysis dataset (n = 425) |
|-----------|----------------------------------|
| Continuous, mean (SD) | |
| Age, years | 49.86 (13.20) |
| Albumin, g/dL | 3.92 (0.58) |
| BMI, kg/m² | 24.62 (4.77) |
| Creatinine clearance, mL/min | 98.31 (32.13) |
| Weight, kg | 70.53 (16.89) |
| Categorical, n (%) | |
| Sex, female | 191 (45) |
| Race | |
| White | 220 (52) |
| Black | 32 (8) |
| Asian | 113 (27) |
| Other | 29 (7) |
| No PPI use | 402 (95) |
| Baseline renal impairment | |
| A, normal | 243 (57) |
| B, mild | 130 (31) |
| C, moderate | 51 (12) |
| D, severe | 1 (0) |
| Baseline hepatic impairment | |
| A, normal | 365 (86) |
| B1, mild | 50 (12) |
| B2, mild | 10 (2) |
| C–D, moderate–severe | 0 (0) |
| CYP2C19 phenotype | |
| Poor | 18 (4) |
| Intermediate | 100 (24) |
| Extensive | 153 (36) |
| Ultra-rapid | 7 (2) |
| CYP2C9 phenotype | |
| Poor | 5 (1) |
| Intermediate | 62 (15) |
| Extensive | 211 (50) |
| Ultra-rapid | 0 (0) |
| CYP3A5 phenotype | |
| Poor | 195 (46) |
| Intermediate | 66 (16) |
| Extensive | 17 (4) |
| Ultra-rapid | 0 (0) |

BMI, body mass index; CYP, cytochrome P450; PopPK, population pharmacokinetic; PPI, proton pump inhibitor.
BALB of 3.2 mg/dL and no PPI use), the final PopPK model predicted a decrease in CL of 26.5%, a decrease in $V_2$ of 28.6%, and unchanged $k_a$ compared with a typical patient.

Sensitivity analysis conducted using 500 simulated profiles from the final PopPK model supported the conclusion that the identified significant covariates on lorlatinib CL did not have a clinically meaningful impact on lorlatinib plasma exposure, with all model-simulated values falling within the predefined clinical no-effect boundary, suggesting that no dose adjustments were required (Figure 3).

**Effect of hepatic and renal impairment on lorlatinib PK**

Although the hepatic function indicators BALT and BBIL were not statistically significant covariates and were not included in the final model, the effect of hepatic function on lorlatinib CL was assessed by summarizing individual estimates of lorlatinib CL in each baseline NCI hepatic impairment group. Within the range of hepatic impairment in the pooled dataset, no changes in lorlatinib CL were predicted with worsening hepatic impairment after either single or multiple doses (Table S1).

To assess possible relationships between renal impairment and lorlatinib CL, individual estimates of lorlatinib CL were summarized by renal impairment group as defined by Kidney Disease Outcome Quality Initiative (KDOQI) staging. There was a trend of decreasing median and mean individual estimates of single dose and steady-state lorlatinib CL with worsening renal function, although ranges overlapped in patients with mild or moderate renal impairment and patients with normal renal function (Table S2).

**DISCUSSION**

Lorlatinib plasma PK was well-characterized by a two-compartment model with CL estimated using an initial CL after

### Table 4 Final PopPK model parameter estimates

| Parameter | Model results | Bootstrap results |
|-----------|---------------|------------------|
|          | Value         | CV (%)           | Shrinkage (%)  | Mean    | 95% CI                  |
| $\theta_{\text{CLI}(L/h)}$ | 9.035         | –                | –              | 9.088   | (8.0115–10.0609) |
| $\theta_{V_2(L)}$ | 120.511       | –                | –              | 120.618 | (103.3633–137.6947) |
| $\theta_{k_a(h^{-1})}$ | 3.113         | –                | –              | 3.128   | (2.3125–3.9145) |
| $\theta_{Q(L/h)}$ | 22.002        | –                | –              | 22.491  | (17.6495–26.3563) |
| $\theta_{V_3(L)}$ | 154.905       | –                | –              | 156.640 | (134.2215–175.6205) |
| $\theta_{\text{IND}}$ | 0.020         | –                | –              | 0.027   | (–0.2136 to 0.2535) |
| $\theta_{D_1(h)}$ | 1.148         | –                | –              | 1.149   | (1.0344–1.2611) |
| $\theta_{F}$ | 0.759         | –                | –              | 0.764   | (0.6728–0.8462) |
| $\theta_{\text{CLMX}(L/h)}$ | 14.472        | –                | –              | 14.584  | (12.7286–16.2186) |
| $\theta_{\text{Res Error for IV}}$ | 0.115         | –                | –              | 0.110   | (0.0811–0.1487) |
| $\theta_{\text{Res Error for PO}}$ | 0.438         | –                | –              | 0.437   | (0.4090–0.4670) |
| $\theta_{\text{BALB on CL}}$ | 0.067         | –                | –              | 0.069   | (0.0214–0.1122) |
| $\theta_{\text{TDOSE on CL}}$ | 0.001         | –                | –              | 0.001   | (0.0004–0.0023) |
| $\theta_{\text{WNCL on CL}}$ | 0.235         | –                | –              | 0.240   | (0.1457–0.3238) |
| $\theta_{\text{PPI on } k_a}$ | –0.675        | –                | –              | –0.664  | (–0.8508 to –0.4986) |
| $\omega_{\text{CL}}^2$ | 0.030         | 17.201           | 23.212         | 0.030   | (0.0159–0.0433) |
| $\omega_{\text{CLMX}(L/h)}^2$ | –0.006        | 7.460            | –              | –0.005  | (–0.0173 to 0.0061) |
| $\omega_F^2$ | 0.022         | 14.964           | 40.174         | 0.023   | (0.0027–0.0420) |
| $\omega_{V_2}^2$ | 0.086         | 29.268           | 52.835         | 0.085   | (0.0430–0.1284) |
| $\omega_{V_3}^2$ | –0.017        | 12.881           | –              | –0.017  | (–0.0492 to 0.0160) |
| $\omega_{V_3}^2$ | 0.101         | 31.742           | 53.123         | 0.099   | (0.0513–0.1502) |
| $\omega_{k_a}^2$ | 2.329         | 152.626          | 45.113         | 2.345   | (1.5982–3.0608) |

The mean and 95% CIs were generated from a bootstrap run of 1,000 resampled datasets, including runs with successful minimization and failed SCOV steps.

BALB, baseline albumin; CL, confidence interval; CLI, initial clearance; CLMX, maximum induced clearance at steady state; CV, coefficient of variation; D1, zero-order duration of absorption; F, bioavailability; h, hour; IIV, interindividual variability; IND, rate constant of induction; $k_a$, rate constant of absorption; PPI, proton pump inhibitor use; Q, intercompartmental clearance; RSE, relative standard error; TDOSE, total daily dose (mg); V2, central volume of distribution; V3, peripheral volume of distribution; WNCL, baseline standardized creatinine clearance.
**FIGURE 1** Plots of (a) observed vs. predicted population and individual lorlatinib plasma concentrations and (b) conditional residuals versus time after first dose and population predicted values from the final lorlatinib population pharmacokinetic (PopPK) model. In Panel a, the red dashed line represents unity and black line represents linear smooth. Dose is in milligrams. CWRES, conditional weighted residuals; log, natural log; IWRES, individual weighted residuals; TAFD, time after first dose.
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A single dose, and a time-varying induced CL after multiple doses. The time-varying, induced CL approached its maximum value at steady-state. To improve $C_{\text{max}}$ estimation, the final model employed a sequential zero-first order absorption process. Two-compartment PopPK models incorporating time-varying clearance mechanisms and PopPK models utilizing sequential zero-first order absorption have been previously described in the literature.\textsuperscript{17–21}

Clearance was evaluated using concentration-dependent saturable clearance, and models linking single-dose and time-dependent clearance. However, successful minimization and variance covariance steps were not achieved. This was likely due to the limitations in the available PK data on different days following multiple dosing, with an absence of PK data available between day 1 and day 15 to characterize the transition from single dose to steady-state lorlatinib clearance.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Prediction-corrected visual predictive check of the final population pharmacokinetic (PopPK) model for (a) all patient data, (b) First 120 hours (both patients and healthy participants), and (c) Day 15 of cycle 1 (patients only). TAFD was reset on period 1 day 1 and thus the first 120 hours represents a pooling of day $-7$ and period 1 day 1. Shaded areas represent a simulation based 90% prediction interval of the 5th, 50th, and 95th percentile of the simulated data. Red lines represent the 5th, 50th, and 95th percentile of the observed data. h, hour; PTST, patient status: 0 for healthy participant, 1 for patients; TAFD, time after first dose.}
\end{figure}
Lorlatinib TDOSE was found to be a statistically significant covariate for lorlatinib CL, which is to be expected for a drug undergoing concentration-related (and dose-related) auto-induction. This was also consistent with lorlatinib plasma exposures estimated by noncompartmental analysis. In Study B7461001, the steady-state lorlatinib CL increased with increasing dose.\textsuperscript{7} In this analysis, initial and time-varying induced CL was reduced by 12.4% with 10 mg q.d. lorlatinib and increased by 13.8% with 200 mg q.d. lorlatinib, compared with individuals receiving 100 mg q.d. lorlatinib. This dose nonlinearity is likely due to an increase in potency of induction with increasing dose, which was accounted for with TDOSE as a covariate on CL.

BALB was also found to be statistically significant on CL. With every unit of BALB over 4 mg/dL, there was a 6.68% increase in CL. For individuals with a BALB value of 3.2 mg/dL, the clearance was 5.3% lower compared with the typical patient with 4 mg/dL of BALB. At a BALB value of 4.6 mg/dL, the clearance was increased 4% compared with the typical patient. Although the exact reason for this relationship is unknown, it is possible that BALB acts as a predictor of a patient’s overall health, with poorer health resulting in impaired drug clearance.

The impact of PPI use was modeled only on the first-order absorption component of the final PopPK model and was found to be associated with a 67.5% decrease in $k_a$. This was consistent with the results of the formal drug interaction study B7461008 in healthy participants, where PPI use decreased $C_{\text{max}}$ by 30% without changing the area under the curve over infinity (AUC\textsubscript{inf}).\textsuperscript{11}
As lorlatinib is extensively metabolized in the liver, the effects of hepatic impairment on lorlatinib PK were also assessed. Hepatic impairment was not found to be a statistically significant covariate in the final model and no correlation was found between baseline NCI hepatic impairment stage and lorlatinib clearance.

There is evidence that chronic or severe renal impairment can also influence the PK of drugs that are exclusively metabolized by the liver. Renal impairment can change levels of serum albumin, affecting the fraction unbound to protein in plasma for a drug and thereby altering its volume of distribution. In addition, chronic renal failure has been shown to reduce CYP activity. Thus, renal impairment as measured by WNLCL was tested as a potential covariate on lorlatinib V2, CL, and F, and was found to be statistically significant on CL in the final model.

A clinically meaningful change in lorlatinib exposure was considered as one that would require a dose adjustment. In the dose escalation portion of Study B7461001, dose-limiting toxicities were seen at the 150 mg q.d. dose and 100 mg q.d. was the recommended phase II dose. Furthermore, whereas the next lower dose from 100 mg q.d. (i.e., 75 mg q.d.) has been associated with plasma lorlatinib concentrations that cover in vitro efficacious concentration targets, the majority of the lorlatinib clinical experience has been at the 100 mg q.d. dose level, which has been shown to be safe and efficacious. Thus, a clinical no-effect boundary was defined as 70–142.9% (30% change on the log scale) as compared with 100 mg q.d., with the lower bound as the exposure at 75 mg q.d. and an upper bound as the exposure at 150 mg q.d. Based on this clinical no-effect boundary, none of the covariate effects identified as statistically significant in the PopPK model were seen to be associated with clinically meaningful changes in lorlatinib plasma exposure. Hence, these findings support current lorlatinib dosing guidelines, which do not recommend dose modifications based on PPI use, age, weight, race, renal and hepatic impairment, BALB, and CYP3A5 and CYP2C9 metabolizer phenotype. As only one patient in the analysis had severe renal impairment, conclusions cannot be made regarding dose recommendations in this patient population.

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CONFLICT OF INTEREST
J.C., B.H., Y.K.P., and A.R.-G. are current or former employees of Pfizer. J.C. and Y.K.P. also own Pfizer stock.

AUTHOR CONTRIBUTIONS
J.C., B.H., Y.K.P., and A.R.-G. wrote the manuscript and designed the research. J.C. and Y.K.P. performed the research. J.C. and B.H. analyzed the data.

DATA AVAILABILITY STATEMENT
Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trial/s/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 the European Union or (2) in programs that have been terminated (i.e., 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 requestors must enter into a data access agreement with Pfizer Inc.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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