

## ARTICLE

# Erdafitinib's effect on serum phosphate justifies its pharmacodynamically guided dosing in patients with cancer

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## Abstract

A population pharmacokinetic (PK)–pharmacodynamic (PD) model was developed using data from 345 patients with cancer. The population PK-PD model evaluated the effect of erdafitinib total and free plasma concentrations on serum phosphate concentrations after once-daily oral continuous (0.5–12 mg) and intermittent (10–12 mg for 7 days on/7 days off) dosing, and investigated the potential covariates affecting erdafitinib-related changes in serum phosphate levels. Phosphate is used as a biomarker for erdafitinib's efficacy and safety: increases in serum phosphate were observed after dosing with erdafitinib, which were associated with fibroblast growth factor receptor target engagement via inhibition of renal fibroblast growth factor 23–mediated signaling. PK-PD model-based simulations were performed to assess the approved PD-guided dosing algorithm of erdafitinib (8 mg once-daily continuous dosing, with up-titration to 9 mg based on phosphate levels [ $<5.5$  mg/dl] and tolerability at 14–21 days of treatment). The serum phosphate concentrations increased after the first dose and reached near maximal level after 14 days of continuous treatment. Serum phosphate increased with erdafitinib free drug concentrations: doubling the free concentration resulted in a 1.8-fold increase in drug-related phosphate changes. Dose adjustment after at least 14 days of dosing was supported by achievement of  $>95\%$  maximal serum phosphate concentration. The peak-to-trough fluctuation within a dosing interval was limited for serum phosphate concentrations (5.68–5.65 mg/dl on Day 14), supporting phosphate monitoring at any time relative to dosing. Baseline phosphate was higher in women, otherwise, none of the investigated covariate–parameter relationships were considered clinically relevant. Simulations suggest that the starting dose of 8-mg with up-titration to 9-mg on Days 14–21 maximized the number of patients within the target serum phosphate concentrations

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(5.5–7 mg/dl) while limiting the number of treatment interruptions. The findings from the PK-PD model provided a detailed understanding of the erdafitinib concentration-related phosphate changes over time, which supports erdafitinib's dosing algorithm.

### Study Highlights

#### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Treatment of advanced urothelial cancer in adult patients with erdafitinib is individualized based on the biomarker serum phosphate and tolerability.

#### WHAT QUESTION DID THIS STUDY ADDRESS?

This study evaluated the effect of erdafitinib pharmacokinetics on serum phosphate over time in a quantitative manner. It addressed whether the starting dose, up-titrated dose, and time of up-titration was adequate and whether dose adjustments based on patient's demographics (e.g., age, sex, Eastern Cooperative Oncology Group status) were necessary.

#### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study supported that individualizing erdafitinib dose based on serum phosphate concentration using the approved dosing algorithm was adequate. No adjustments based on demographic characteristics were recommended.

#### HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This example is a further step toward individualized dosing, which is achieved through identification and quantification of biomarker relationships with pharmacokinetics, efficacy, and safety.

## INTRODUCTION

The fibroblast growth factor receptor (FGFR) tyrosine kinase family regulates a number of key cellular processes. Abnormal activation of FGFR signaling pathways plays a crucial role in tumor cell proliferation, angiogenesis, migration, and survival,<sup>1–3</sup> thereby making inhibition of FGFR activation an attractive target for anticancer agents.

A potent, oral selective pan-FGFR tyrosine kinase inhibitor, erdafitinib (Balversa®, Janssen Pharmaceutical Companies), received accelerated US Food and Drug Administration approval in April 2019 for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma and susceptible FGFR3 or FGFR2 genetic alterations that progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy,<sup>4</sup> and is currently being evaluated further in phase II and III studies in patients with urothelial and other cancers.

Owing to erdafitinib's mechanism of action and its inhibition of renal fibroblast growth factor 23-mediated signaling, an increase in serum phosphate concentrations was observed after dosing with erdafitinib, which was associated with FGFR target engagement. Specifically, FGFR loss of function counteracts renal fibroblast growth

factor 23/Klotho signaling, leading to the deregulation of cytochrome P450 (CYP) 27B1 and CYP24A1 and the induction of hypervitaminosis D. As a consequence, hyperphosphatemia is an expected toxicity of FGFR inhibitors based on their mechanism of action and has been seen in studies of erdafitinib as well as with other selective FGFR inhibitor small molecule kinase inhibitors.<sup>5–7</sup> Serum phosphate is considered a pharmacodynamic (PD) biomarker of efficacy and safety for erdafitinib. Target phosphate levels were selected during erdafitinib development based on emerging data from phase I<sup>7</sup> and phase II<sup>8</sup> trials as well as pharmacokinetic (PK)–PD modeling based on these data. They were further supported by exposure–response analysis of the pivotal phase II study. Namely, outcomes in patients receiving the recommended dose regimen in the BLC2001 study (Regimen 3) and achieving phosphate concentrations  $\geq 5.5$  mg/dl within 3 months versus those who did not were objective response rate (ORR) 43.1% versus 34.6% and median progression-free survival (PFS) 5.59 versus 3.81 months, respectively. The exposure–response analyses further supported the link between phosphate and clinical outcomes, with higher serum phosphate levels within the first 6 weeks showing better PFS (hazard ratio: 0.80 [0.67–0.94] per mg/dl of  $\text{PO}_4$ ;  $p = 0.01$ ) and ORR (odds ratio [OR]: 1.38 [1.02–1.86] per mg/dl of  $\text{PO}_4$ ;  $p = 0.04$ ).<sup>9</sup>

Regarding safety, phosphate concentrations below 7 mg/dl were considered of no clinical concern in terms of longer term sequelae, whereas 9 mg/dl was considered the threshold for acute hyperphosphatemia. These safety thresholds and the associated dose modifications were originally established based on the clinical definition of the normal range (up to 4.5 mg/dl) and were then considered adequate based on study results showing 34.3% of BLC2001 Regimen 3 patients experiencing treatment-emergent adverse events considered potential sequelae of prolonged hyperphosphatemia (such as anemia, hypotension, and hypercalcemia, among others). The effect of phosphate levels on safety was also supported by the exposure–response analysis, with the largest effect of phosphate for nail (OR: 2.84 [1.87–4.31] per mg/dl of phosphate [ $\text{PO}_4$ ];  $p < 0.001$ ) and eye disorders (OR: 2.44 [1.65–3.62] per mg/dl of  $\text{PO}_4$ ;  $p < 0.001$ ) relative to skin disorders, hand–foot syndrome, and central retinopathy.<sup>9</sup> Various dose levels, dosing regimens, and individualized up or down dose titrations based on serum phosphate concentrations were evaluated.

A population PK model describing total and free erdafitinib plasma concentration–time profiles was developed based on pooled single and repeated dose data in 373 healthy subjects and patients with cancer from six phase I and II studies.<sup>10</sup> The PK of erdafitinib were linear and time independent. Erdafitinib is highly bound to  $\alpha$ -1 glycoprotein acid, which varies with health status. Fraction unbound (FU) is highly variable, with a mean (SD) of 0.29 (0.18) in the target population. Protein binding was integrated in the population PK model of erdafitinib. Following oral administration of the tablet formulation, erdafitinib was rapidly absorbed, with a time to maximum concentration of 2–4 h post dose. Erdafitinib free apparent oral clearance was 83.2 L/h, which translated into a total apparent oral clearance of 0.200 L/h for the mean FU of 0.24% observed in the target population. Effective terminal half-life of the total drug was 76.4 h. After approximately 14 days, more than 94% of steady-state exposure of erdafitinib is reached following once-daily (q.d.) dosing, with approximately a 5.1-fold accumulation of erdafitinib area under the concentration–time curve from time 0 to 24 hours ( $\text{AUC}_{0-24}$ ).

The aim of the present analysis was to characterize the concentration–time profile of serum phosphate after erdafitinib administration. A PK–PD model was developed based on the previously developed population PK model<sup>10</sup> and plasma PK and serum phosphate concentration data from all 345 patients with cancer included in the population PK analysis. The population PK–PD model was developed to assess the effect of erdafitinib total and free plasma concentrations on serum phosphate concentrations at continuous and intermittent

(7 days on, 7 days off) dosing and to provide a quantitative assessment of the potential effect of covariates on erdafitinib-related changes in serum phosphate levels in patients with cancer.

In addition, PK–PD model-based simulations were performed to evaluate the PD response following the approved regimen of a continuous regimen of 8 mg q.d. with potential up-titration to 9 mg q.d. if the phosphate concentration measured between Day 14 and Day 21 was  $< 5.5$  mg/dl and there was no significant treatment-related toxicity. The effects of the starting dose level and the time and dose level for up-titration as well as potential covariates were investigated to evaluate the recommended PD-guided regimen.

## METHODS

### Patients and study design

PK (total and free erdafitinib plasma concentrations) and PD (serum phosphate concentrations) data from the following three studies conducted in patients with cancer were used for this analysis: (1) EDI1001 (NCT01703481), a first-in-human multiple dose, phase I study to evaluate the safety, PK, and PD of erdafitinib and to identify dosing for phase II studies<sup>7</sup>; (2) BLC2001 (NCT02365597), a multiple-dose, open-label, phase II study to determine the efficacy and safety of continuous versus intermittent dosing in patients with metastatic or unresectable urothelial carcinoma and select FGFR genomic alterations<sup>8</sup>; and (3) GAC1001 (NCT01962532), a multiple dose phase I study to evaluate the safety, PK, and PD of erdafitinib in Japanese patients.<sup>11</sup> Details of the study designs, sample sizes, dosing regimens, and sampling schedules of these studies were described previously<sup>10</sup> and are summarized in Table S1.

Institutional review boards approved the study protocols and amendments. The studies were conducted in accordance with the ethical principles originating in the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. Participants provided written informed consent before participating in the study.

### PK–PD analysis

#### Bioanalytical procedures

Plasma concentrations of erdafitinib were quantified using validated nonchiral liquid chromatography–mass spectrometry assays in the bioanalytic laboratory of

Janssen R&D, a division of Janssen Pharmaceutica in Beerse, Belgium, and at a contract research organization, PRA Health Sciences in Assen, the Netherlands. Plasma protein binding was determined in the bioanalytic laboratory of Janssen R&D through equilibrium dialysis. Details of these bioanalytic procedures were reported previously.<sup>10</sup> Serum phosphate concentrations were measured at the study sites. The fact that phosphate values were measured at the study site and not in a central laboratory, although having the advantage of fast turnaround for patient follow-up, might have increased variability and/or bias. However, results showed that residual variability from the model was low on serum phosphate (11.9%). In addition, phosphate measurements are expected to be relatively consistent between laboratories because of its inorganic nature and routine use.

## Model development

A population PK-PD model assessing the relationship between erdafitinib plasma concentrations and serum phosphate concentrations was developed based on the clinical data. Post hoc Bayesian individual PK parameters were obtained from the previously developed population PK model and used to generate the erdafitinib concentration-time profile during the PK-PD analysis, consistent with sequential modeling methodology proposed by Zhang et al.<sup>12</sup>

Based on a preliminary exploration, the starting model for the relationship between the absolute change from baseline ( $[\text{PO}_4]_{\text{BSL}}$ ) in serum phosphate concentrations and free erdafitinib plasma concentrations in the biophase ( $C_e$ ) was a linear model (slope  $M$ ). This relationship was also investigated using total erdafitinib plasma concentrations as well as with other type of models (e.g., maximum effect  $[E_{\text{max}}]$  model). Serum phosphate concentrations at time  $t$  ( $[\text{PO}_4]_t$ ) were described in Equations (1) and (2):

$$[\text{PO}_4]_t = [\text{PO}_4]_{\text{BSL}} + M \cdot C_e \quad (1)$$

With

$$\frac{dC_e}{dt} = k_{e0} \cdot C - k_{e0} \cdot C_e \quad (2)$$

where  $C$  was the erdafitinib concentration in the central compartment and  $k_{e0}$  was the effect compartment rate constant that accounts for the delay between central compartment concentration and PD effect.<sup>13</sup> Phosphate baseline was estimated as a model parameter.

Graphical exploration of the data suggested that serum phosphate concentrations following erdafitinib dosing may decrease over time after initially reaching steady state. Therefore, an exploration of the time-dependent PD was conducted using empirical and semimechanistic models. Such models were included as modifications of the drug effect over time through empirical functions or through an indirect response model.

The interindividual variability (IIV) in model parameters was assumed to follow a log-normal distribution, except for serum phosphate at baseline, where a normal distribution was also investigated. Residual variability was evaluated using an additive error model after natural logarithmic transformation of the measured concentrations and model predictions.

## Covariate analysis

The PK-PD model was used to conduct a covariate analysis on the PD parameters. Baseline covariates evaluated were sex, age, race, renal impairment, hemoglobin levels, phosphate binder intake, FGFR positive (FGFR+) tumors, FGFR alterations, cancer type (urothelial vs. nonurothelial), Eastern Cooperative Oncology Group status, disease distribution (presence or absence of visceral metastases), and pretreatment status (chemotherapy naïve vs. chemotherapy relapsed/refractory). In a first step, plots of the post hoc estimates of the random effects of the PD model parameters against the continuous and categorical covariates selected for evaluation were performed. The  $r^2$  and  $p$  value of each covariate-parameter relationship was examined, and covariate-parameter relationships with  $r^2$  above 0.15 and a  $p$  value below 0.001 were selected for a second step, that is, a formal stepwise covariate analysis.

## Model selection and evaluation

In the selection of a preferable model, models that converged successfully had a successful estimation of the standard errors, produced reasonable parameter estimates, and had low IIV and low correlations among random effects were preferred over others.

The improvement in the fit obtained was assessed by examination of the change in the objective function value (a drop of  $\geq 10.83$  points was required to reach statistical significance for the addition of one fixed effect;  $p = 0.001$ ) and goodness-of-fit plots. The Bayesian information criterion (BIC) and Akaike information criterion (AIC) were used for comparisons of non-nested models. Evaluation of the PK-PD model was performed using prediction-corrected visual predictive checks.<sup>14,15</sup>

## PK-PD model-based simulations

The population PK-PD model was used to simulate PK and serum phosphate concentrations in FGFR+ urothelial patients with cancer. A virtual population of 1000 or 10,000 (for the covariate effects scenarios) random virtual patients were sampled from the final PK-PD model parameter distributions. Parameter uncertainty was not taken into account in the simulations as its impact compared with that of IIV was deemed minor.<sup>16</sup>

Various simulation scenarios were compared relative to the approved PD-guided dosing algorithm used as the reference. In the approved dosing regimen, patients started erdafitinib treatment at 8 mg q.d. and were eligible for up-titration to 9 mg q.d. on Days 14–21 if the serum phosphate concentration was below 5.5 mg/dl. The rationale for the up-titration time was based on ensuring that the drug effect had reached steady state (i.e., maximum phosphate increase under q.d. dosing) prior to up-titration. This would ensure that the further phosphate increases after up-titration would not cross the 7 mg/dl safety threshold. For simplicity, Day 14 was used as potential up-titration time for all patients in the simulations of the approved dosing regimen. After Day 14, the drug was interrupted whenever phosphate concentrations exceeded 7 mg/dl. Depending on the extent and duration of phosphate elevation, treatment was resumed at the same or at a lower dose once serum phosphate concentrations returned below 5.5 mg/dl. Dose reduction levels were 8 mg q.d. (in case of up-titration to 9 mg), then 6 mg q.d., then 5 mg q.d., and then 4 mg q.d.

Investigated scenarios are summarized in Table 1 and included the approved PD-guided dosing algorithm, fixed-dose regimens, regimens with lower starting doses, and regimens with up-titrations at various timepoints. Different scenarios (including the approved scenario) were also evaluated in case of reduced clearance (e.g., because of drug–drug interactions). For these scenarios, the study design of the pivotal study BLC2001 was reproduced (Table S1). An increase in the up-titration threshold from 5.5 to 7.0 mg/dl was investigated (Scenario 10) to evaluate the changed dose algorithm of the phase III BLC3001 study (NCT03390504). Dose interruption/reduction rules were also modified to account for the modified phosphate thresholds (i.e., dose interruption if phosphate >9 mg/dl instead of 7 mg/dl previously, and dose reductions based on the 9 mg/dl interruption threshold). Lastly, the approved regimen scenario was used to investigate whether the individualized algorithm helped to control potential PK and PD differences due to the effect of subject specific covariates (intrinsic factors) on PK or PD model parameters. Following covariates were investigated: age (66–75 years, >75 years vs. <65 years), weight (<60 kg, >80 kg vs. 60–80 kg), sex (female vs. male), race (White Hispanic, Asian, other vs. White non-Hispanic), renal impairment (mild and moderate impairment vs. normal function), and hepatic impairment (mild impairment vs. normal function).

The clinically relevant metrics used to compare simulated data of each scenario included the proportion of patients achieving target phosphate concentrations (5.5–7 mg/dl at the time of analysis), the proportion of patients on different dose levels (4, 5, 6, 8, or 9 mg), the dose

**TABLE 1** Summary of simulation scenarios

Scenario	Description	Starting dose	Up-titration dose	Time of up-titration	Investigated aspect
Reference	BLC2001 Regimen 3 (approved dosing regimen)	8 mg	9 mg	Day 14	Covariates
1	6 mg q.d., no up-titration	6 mg	NA	Day 14	Starting dose and up-titration
2	8 mg q.d., no up-titration	8 mg	NA	Day 14	
3	9 mg q.d., no up-titration	9 mg	NA	Day 14	
4	6 mg starting dose, up-titration	6 mg	8 mg	Day 14	Starting dose
5	Reference with titration Day 21	8 mg	9 mg	Day 21	Timing of up-titration
6	Reference with titration Day 28	8 mg	9 mg	Day 28	
7	33% lower clearance	8 mg	9 mg	Day 14	Potential interactions
8	33% lower clearance, 5 mg starting dose	5 mg	6 mg	Day 14	
9	33% lower clearance, 6 mg starting dose	6 mg	8 mg	Day 14	
10	BLC3001 dosing regimen	8 mg	9 mg	Day 14	New phosphate thresholds

Note: BLC2001 Regimen 3 = 8 mg starting dose, BLC3001 dosing regimen = 8 mg starting dose, up-titration to 9 mg at Cycle 1, Day 14 if serum phosphate is below 7.0 mg/dl.

Abbreviation: NA, not applicable; q.d., once daily.

intensity (% of full compliant dose), and the number of dose interruptions and adaptations.

The PK-PD analysis was performed in accordance with appropriate guidelines.<sup>17</sup> The PK and PD concentration-time data were used for nonlinear mixed effect modeling using NONMEM® Version 7.3.0 (ICON plc), compiled by Fortran 64 Compiler Professional (Intel Corporation, USA), Version 11.1. The first-order conditional estimation method with interaction was used. Exploratory analysis, diagnostic plots, and the post-processing of the NONMEM analysis results were carried out in R Version 3.4.1 (Comprehensive R Network, <http://cran.r-project.org/>). Simulations were performed using Simulo Expert 7.2 (SGS Exprimio, Belgium) and post-processed using R (Version 3.4.3).

## RESULTS

### Population

A total of 4639 total serum phosphate concentrations from 345 patients who received continuous q.d. doses (range, 0.5–12 mg) or intermittent (7 days on, 7 days off) q.d. doses (range, 10–12 mg) of erdafitinib were available for analysis. The demographic characteristics of these patients are summarized in Table 2. Observed serum phosphate concentrations versus time since first dose (during the first 6 months of treatment) are presented in Figure 1. The longest phosphate follow-up was 104 weeks after the first dose of erdafitinib.

### PK-PD analyses

The final PK-PD model was characterized by a slope model, with a coefficient ( $M$ ) and an exponent ( $\gamma$ ) (Equation 3). The estimated relationship was close to linear, with an exponent of 0.86. Free concentrations at biophase correlated better with serum phosphate than total erdafitinib concentrations. This was confirmed by the lower BIC and AIC as well as an absolute reduction of 15% in the IIV on drug effect when using free instead of total concentrations for comparable models. The estimated delay between plasma and phosphate concentration changes was moderate, with an equilibration half-life of 34.5 h. The effect compartment was also relevant to capture IIV, estimated at 90.9% for the effect compartment rate constant. Indirect response models did not provide better fits to the data than the effect compartment model. This might be partly due to the time to maximum effect not increasing with dose in the available data.

$$[\text{PO}_4]_t = [\text{PO}_4]_{\text{BSL}} + M \cdot C_e^\gamma \quad (3)$$

Phosphate data pointed toward an attenuation of the drug effect on phosphate over time. This effect was empirically modelled by a time-dependent function of slope  $M$  (Equation 4):

$$M = m \cdot (1 - T), \quad \text{where } \frac{dT}{dt} = k_{\text{in}} \cdot (1 - T) \quad (4)$$

where  $T$  was the amount of attenuation over time,  $k_{\text{in}}$  was the rate constant describing the attenuation of drug effect with time, and  $m$  was the coefficient of the slope model describing the relationship between  $[\text{PO}_4]$  and  $C_e$  at time 0. This attenuation was not correlated with erdafitinib concentrations. Based on clinical data, it was also estimated that approximately 580 h (24 days) after the last dose of erdafitinib a posttreatment baseline phosphate concentration was reestablished at 2.67 mg/dl, lower than the pretreatment baseline of 3.08 mg/dl (Figure 2). This was accounted for using an empirical time-dependent function of  $[\text{PO}_4]_{\text{BSL}}$  (Equations 5 and 6):

$$[\text{PO}_4]_{\text{BSL}} = [\text{PO}_4]_0 \quad \text{if } (T_{\text{SLD}} \leq t_{\text{lag}}) \quad (5)$$

$$[\text{PO}_4]_{\text{BSL}} = [\text{PO}_4]_{\text{P}} - ([\text{PO}_4]_{\text{P}} - [\text{PO}_4]_0) \cdot e^{-k_{\text{base}} \cdot (T_{\text{SLD}} - t_{\text{lag}})} \quad \text{if } (T_{\text{SLD}} > t_{\text{lag}}) \quad (6)$$

where  $[\text{PO}_4]_0$  was the population estimate of the phosphate baseline value when  $T_{\text{SLD}}$  was less or equal to  $t_{\text{lag}}$  (pretreatment baseline),  $T_{\text{SLD}}$  was the time since last dose,  $[\text{PO}_4]_{\text{P}}$  was the estimate of the phosphate baseline value plateau,  $k_{\text{base}}$  was the rate of decline of phosphate baseline value with time, and  $t_{\text{lag}}$  was the time delay after which the phosphate baseline value started to decline with time. All parameters were estimated with adequate precision (relative standard errors <13% for fixed effects and <18% for random effects). Serum phosphate concentrations over time were adequately described by the PK-PD model (Figure S1).

The simulated serum phosphate concentration versus time profile for a typical patient under a continuous 8 mg q.d. dosing regimen with and without treatment interruption is displayed in Figure 2a. The time course of erdafitinib free concentrations in plasma and in the biophase as well as the increase in serum phosphate with continuous daily dosing is shown in Figure 2b.

None of the investigated covariate-parameter relationships were identified as significant based on the criteria defined in the Methods section. However, as a sex effect is known to affect phosphate concentrations and as it was

**TABLE 2** Patient characteristics at baseline

Patient characteristics	PK-PD data set (N = 345), mean (SD) [range] or n (%)	Missing data in PK-PD data set, n (%) <sup>a</sup>
Age, years	61.1 (11.9) [21–88]	0 (0.00)
Sex		
Male	190 (55.1)	0 (0.00)
Female	155 (44.9)	
Race/ethnicity		
White	270 (78.3)	0 (0.00)
Caucasian	233 (67.5)	
Hispanic	37 (10.7)	
Black	6 (1.74)	
Asian	37 (10.7)	
Other <sup>b</sup>	32 (9.28)	
Hepatic impairment <sup>c</sup>		
Normal	272 (78.8)	3 (0.870)
Mild	69 (20.0)	
Moderate	1 (0.290)	
Renal impairment <sup>d</sup>		
Normal	114 (33.0)	1 (0.290) <sup>e</sup>
Mild	135 (39.1)	
Moderate	95 (27.5)	
Hemoglobin, g/dl	11.8 (1.77) [7.90–16.7]	19 (5.51)
Phosphate baseline, mg/dl	3.31 (0.631) [1.49–5.20]	15 (4.35)
Phosphate binder		
Taken	165 (47.8)	0 (0.00)
Not taken	180 (52.2)	
FGFR positivity		
Positive	248 (71.9)	19 (5.51)
Negative	78 (22.6)	
FGFR alteration		
Mutation	123 (49.6)	
Amplification	51 (20.6)	
Translocation	74 (29.8)	
Cancer type		
Urothelial	153 (44.3)	0 (0.00)
Nonurothelial	192 (55.7)	
ECOG		
Grade 0	116 (33.6)	19 (5.51)
Grade 1	192 (55.7)	
Grade 2	18 (5.22)	
Disease distribution		
Visceral metastases	199 (57.7)	19 (5.51)
No visceral metastases	127 (36.8)	

(Continues)

**TABLE 2** (Continued)

Patient characteristics	PK-PD data set (N = 345), mean (SD) [range] or n (%)	Missing data in PK-PD data set, n (%) <sup>a</sup>
Pretreatment status		
Chemotherapy naïve	12 (3.48)	19 (5.51)
Chemotherapy relapsed/refractory	314 (91.0)	
Number of participants		
EDI1001	187 (54.2)	
BLC2001	139 (40.3)	
GAC1001	19 (5.51)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FGFR fibroblast growth factor receptor; PK-PD, pharmacokinetic–pharmacodynamic.

<sup>a</sup>Missing data were imputed for modeling purposes with the median of the nonmissing values (continuous covariates) or the most common category (categorical covariates).

<sup>b</sup>Native Hawaiian, Pacific Islander, American Indian, or Alaskan Native, other, multiple and race = White but without known ethnicity (Caucasian or Hispanic).

<sup>c</sup>Classification for hepatic impairment based on National Cancer Institute.

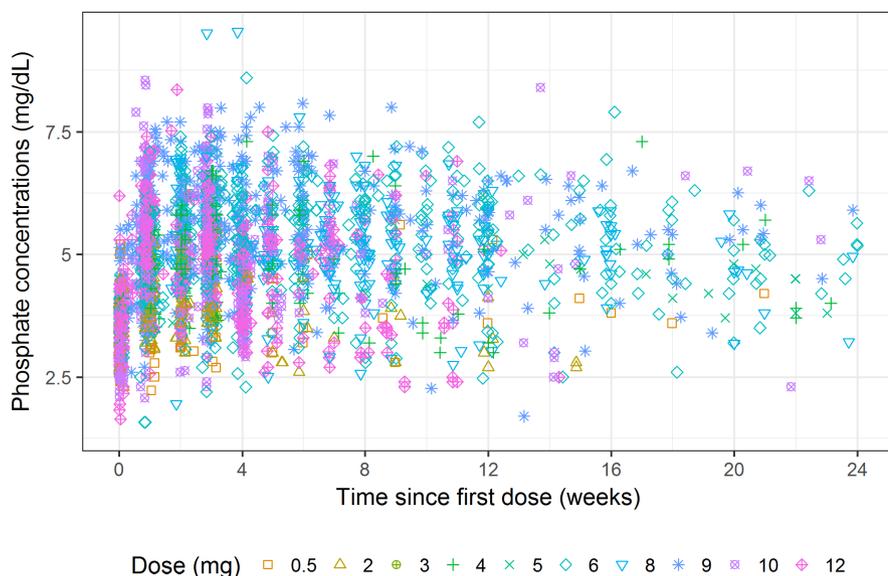
<sup>d</sup>Classification for renal impairment based on estimated glomerular filtration rate–Modification of Diet in Renal Disease.

<sup>e</sup>One subject had missing non-normalized estimated glomerular filtration rate (ml/min/1.73 m<sup>2</sup>) and two subjects had missing body surface area, leading to three subjects with missing body surface area–normalized estimated glomerular filtration rate but only one subject with missing renal impairment.

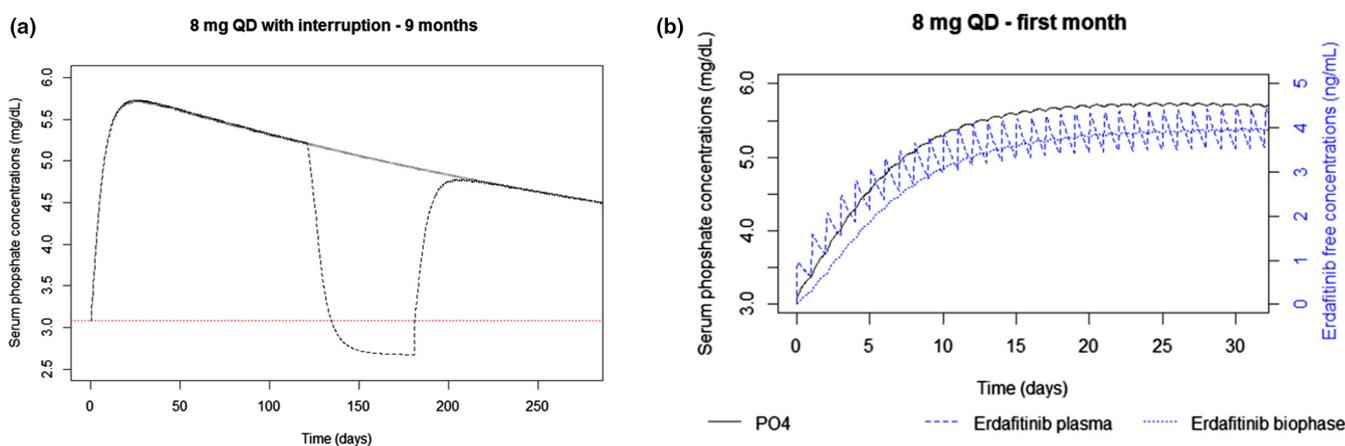
the covariate with the highest  $r^2$  (0.09), sex was included as a covariate on phosphate baseline. Phosphate baseline serum concentrations were 12.4% higher in females compared with males.

## PK-PD model-based simulations

Simulations of phosphate concentrations and proportions of patients at different dose levels over time using the PK-PD model are shown in [Figure 3](#) for the approved PD-guided dosing algorithm. This algorithm predicted to result in 29% of subjects within the phosphate target concentrations range (5.5–7 mg/dl) after Cycles 1 and 4 of treatment. After 4 months of treatment, which corresponded to the median efficacy follow-up of subjects in the approved dose regimen at the time of analysis, 65% of patients were below the target phosphate concentration of 5.5 mg/dl, whereas very few patients were above the safety thresholds (5% and <1% within phosphate concentrations of 7.0–9.0 mg/dl and above 9.0 mg/dl, respectively). Approximately 38% of patients had at least one treatment interruption.



**FIGURE 1** Observed serum phosphate concentrations versus time since first dose (during the first 6 months of treatment). Phosphate concentrations measured during treatment interruptions are not displayed in this plot

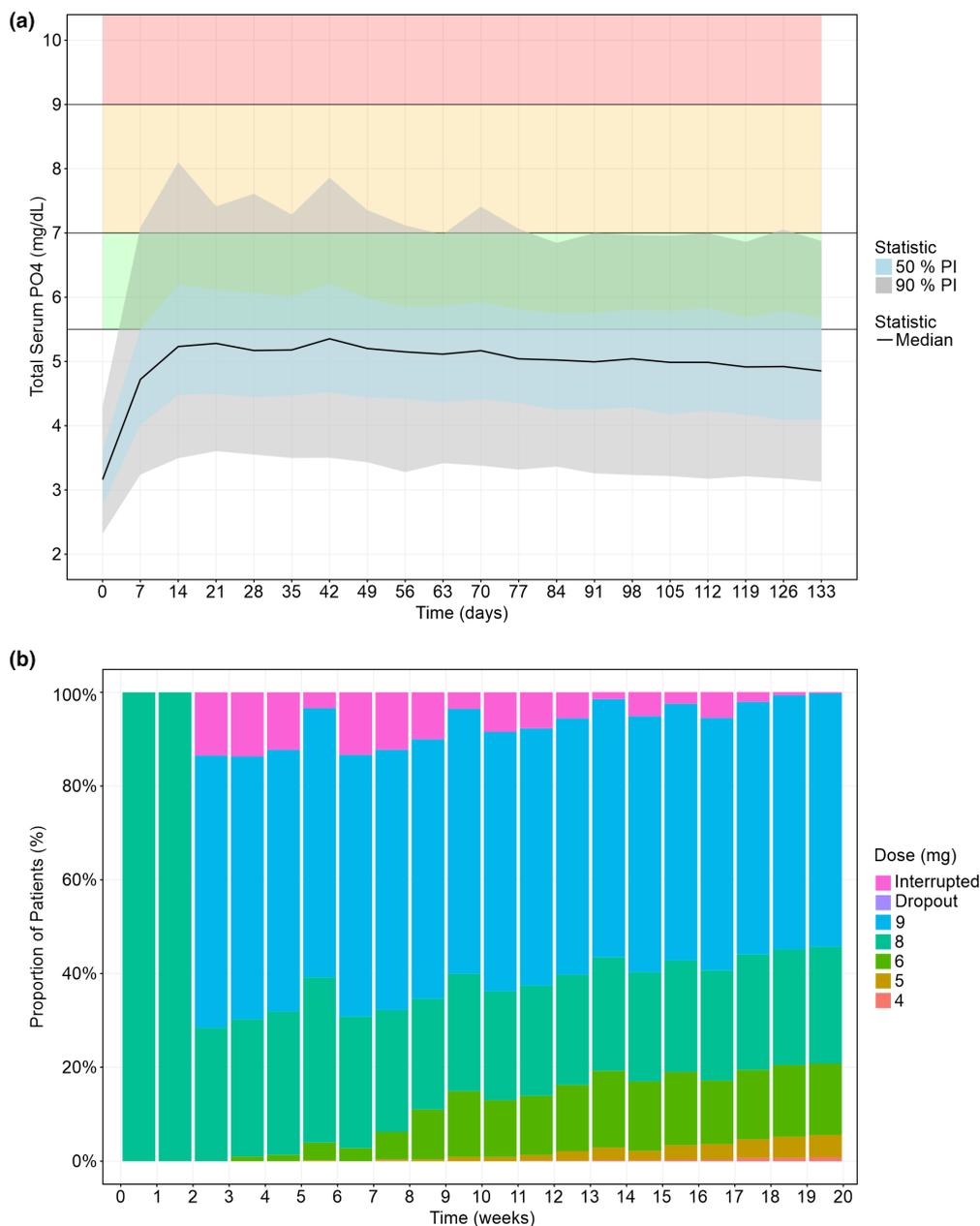


**FIGURE 2** (a) Simulated serum phosphate concentration-time profile for 8 mg once daily with and without interruption at Day 120 for 2 months and then reinitiation at the same dose based on the final pharmacokinetic-pharmacodynamic model. (b) Simulated free erdafitinib plasma concentrations, free erdafitinib concentrations at biophase, and serum phosphate concentrations based on the final pharmacokinetic-pharmacodynamic model (8 mg once daily for 1 month). In **Figure 2a**, the gray solid line represents the deterministic simulations of serum phosphate concentrations for a typical patient receiving 8 mg once daily after 9 months of treatment without interruption. The black dashed line represents the deterministic simulations if this patient is interrupted for 2 months after 4 months of treatment, after which he resumes treatment at 8 mg once daily. The red dashed line represents phosphate baseline. PO<sub>4</sub>, phosphate; QD, once daily

In general, a fixed-dose regimen (Scenarios 1, 2, and 3) was less optimal than the approved PD-guided dosing algorithm (**Table 3**). The fixed dose of 9 mg led to a comparable proportion of subjects within target at the end of Cycle 4; however, the number of subjects having three or more treatment interruptions was increased. This pointed toward potential tolerability issues, which were observed in Study EDI1001 at the 9-mg dose level. A starting dose of 6 mg with potential up-titration to 8 mg (Scenario 4) resulted in less subjects at the target range by Cycle 4 Day 28 (27% vs. 29%). Performing the up-titration later than Day 14 (Day 21 or Day 28; Scenarios 5 and 6) of Cycle 1 resulted in a comparable proportion of subjects within the

serum phosphate target concentrations while leading to lower dose intensity during Weeks 2 and 3 (**Figure S2**). The effect of covariates on PK and PD parameters translated into differences generally lower than 10% in the proportion of subjects in the different serum phosphate ranges after four cycles of treatment. Sex, a covariate in both the PK and PD models, showed the greatest differences, with 57% of females with serum phosphate concentrations <5.5 mg/dl versus 72% of males after four cycles of treatment (**Table S2**).

When simulating a 33% lower erdafitinib oral clearance (Scenario 7), the proportion of subjects having high phosphate concentrations (>7 mg/dl) increased from 5% to 9%,



**FIGURE 3** Simulated serum phosphate concentrations (a) and proportion of patients on different dose levels (b) versus time for the approved pharmacodynamically guided dosing algorithm. Solid black line represents median serum phosphate concentrations. The blue and gray areas are the 50% and 90% prediction intervals (PIs) for serum phosphate concentrations, respectively. The green area represents serum phosphate concentrations between 5.5 and 7 mg/dl, the orange area between 7 and 9 mg/dl, and the red area >9 mg/dl

and the proportion of treatment interruptions on Week 4 of Cycle 4 increased from 5% to 10% compared with the recommended PD-guided dosing algorithm. Using a lower starting dose of 5 mg (Scenario 8) led to results comparable with the recommended dosing algorithm without reduced clearance. Using a lower starting dose of 6 mg (Scenario 9) led to a higher proportion of subjects on target (34% vs. 29%) and a slightly higher proportion of subjects having high phosphate concentrations (>7 mg/dl; 7% vs. 5%) as well as a higher proportion of subjects having dose interruptions (49% vs. 38%, cumulatively over five cycles)

compared with the recommended PD-guided dosing algorithm without reduced clearance. Lastly, increasing the phosphate up-titration threshold (Scenario 10) resulted in a higher proportion of subjects being up-titrated (98% of subjects in comparison of 58% in the reference scenario). Changing target phosphate concentrations can help maximize the percentage of subjects being up-titrated without increasing the number of subjects experiencing at least one treatment interruption (15% in this scenario compared with 38% in the proposed dosing regimen with previous target phosphate concentrations).

**TABLE 3** Proportion of patients within and above target phosphate concentrations for each simulated scenario

Scenario	Description	Percentage in target at C4D28 (efficacy) <sup>a</sup>	Percentage above target at C4D28 (safety) <sup>b</sup>	Interrupted (%)	≥3 Interruptions (%)	Conclusion of simulation
Reference	BLC2001 Regimen 3 (proposed dosing regimen)	29.4	5.1	5.5	38.2	Current dosing algorithm is adequate
1	Fixed dose 6 mg	20.9	2.9	3.0	24.4	Up-titration decreases the risk of hyperphosphatemia
2	Fixed dose 8 mg	27.7	4.7	5.0	35.9	
3	Fixed dose 9 mg	28.8	6.9	7.2	42.6	
4	BLC2001 Regimen 2 (6–8 mg)	26.5	3.4	3.5	30.2	Starting dose of 6 mg too low
5	Time of up-titration Day 21	29.1	5.1	5.4	37.4	Current dosing algorithm is adequate
6	Time of up-titration Day 28	28.8	5.1	5.4	37.4	
7	Lower clearance (by 33%) 8 mg	35.6	9.0	10.4	58.4	Starting dose might be lowered to 5 or 6 mg if clearance decreases (e.g., selected strong CYP inhibitors)
8	Lower clearance (by 33%) 5 mg	27.1	4.8	5.3	35.9	
9	Lower clearance (by 33%) 6 mg	34.1	7.2	8.6	48.7	
10	BLC3001 dosing regimen	39.6	1.8	1.8	14.5	Can help to maximize the percentage of subjects being up-titrated

Abbreviation: C4D28, Cycle 4, Day 28; CYP, cytochrome P450.

<sup>a</sup>Phosphate concentration considered was 5.5–7 mg/dl for Scenarios 1–9 and 5.5–9 mg/dl for Scenario 10.

<sup>b</sup>Phosphate concentration considered was >7 mg/dl for Scenarios 1–9 and >9 mg/dl for Scenario 10.

## DISCUSSION

The primary goal of the erdafitinib population PK-PD analysis was to link erdafitinib plasma concentrations to the time course of serum phosphate concentrations and to quantify the IIV and intraindividual variability of serum phosphate in patients with cancer.

Based on the final PK-PD model, serum phosphate concentrations increased with erdafitinib free drug concentrations: doubling the free concentration resulted in a 1.8-fold increase in drug-related phosphate changes. Thus, serum phosphate concentrations of a typical male individual receiving 8 mg of erdafitinib q.d. would increase from a pretreatment baseline of 3.08 to 5.56 mg/dl on Day 14, within the 5.5 to 7.0 mg/dl target for serum phosphate concentrations. For a typical individual receiving 6 or 9 mg q.d., serum phosphate concentrations would increase from a pretreatment baseline of 3.08 to 5.01 mg/dl and 5.82 mg/dl on Day 14, respectively. With the 6 mg q.d. dosing regimen, the predefined target of 5.5–7.0 mg/dl was not reached for a typical individual contrary to the 8 and 9 mg q.d. regimens. The peak-to-trough fluctuation within a dosing interval was low for serum phosphate concentrations, also supporting the monitoring of phosphate

concentrations at any time during the day for dosage adjustment.

Furthermore, clinical phosphate data suggested an attenuation of the drug effect on phosphate over time. The slope of the modeled drug effect declined with time, with a 50% reduction predicted after 9.5 months. Serum phosphate concentrations started declining after 1 month of treatment, dropping around 1 mg/dl after 9 months following continuous daily dosing at 8 mg. The decrease in serum phosphate concentrations with time could help decrease the potential adverse events related to high phosphate concentrations, if any. The impact of this attenuation of phosphate concentrations with time on clinical efficacy remains unknown and requires further investigation. The lower phosphate concentrations observed after prolonged treatment interruption may be related to phosphate homeostasis because it occurred when erdafitinib concentrations were negligible and seemed to present an important intersubject variability. Because of the limited number of long-term follow-up data after treatment interruption, the behavior of phosphate concentrations after long follow-up is currently uncertain and further investigations would be needed to determine if phosphate concentrations may or may not increase

again to pretreatment baseline. It should be noted that all observed phosphate changes were attributed to drug effect. Some factors known to affect phosphate concentrations and present in a sufficient number of subjects, namely, comedication with phosphate binders (mandated per protocol if phosphate concentration >7 mg/dl) and circadian rhythm, were tested but not found statistically significant in the model. Note that for study conduct, medications known to increase phosphate levels were to be avoided if possible. Other factors potentially affecting phosphate homeostasis (other comedication, infections, diet changes) were not identified in a sufficient number of subjects to be tested. Any such factors, if present, may nevertheless be indirectly accounted for on the individual level through random effects.

PK-PD model-based simulations supported that the starting dose of 8 mg with individualized up-titration to 9 mg on Cycle 1, Day 14 maximized the number of patients with desirable serum phosphate concentrations while limiting the number of treatment interruptions. An increase in the up-titration threshold of serum phosphate as planned for BLC3001 can help to further improve these aspects. Small increases in the proportion of patients in target was considered clinically relevant in this population where limited treatment options are available. The proposed regimen maximized the proportion of patients within the target, whereas patients below the target would still receive benefit from erdafitinib. In addition, preliminary exposure–response analysis supports that even small changes in phosphate concentrations may have a relevant impact on clinical end points such as ORR, PFS, and overall survival. Lastly, the mentioned analysis supported the use of absolute phosphate concentrations over that of, for example, relative changes from baseline.

The simulations confirmed that age, race, weight, hepatic impairment, and renal impairment were adequately corrected by the PD-guided dose adjustment. Sex differences were predominantly due to the difference in baseline phosphate rather than differences in exposure, with females having a phosphate baseline on average 0.37 mg/dl higher than males. However, based on the PK-PD model, the relative increase in phosphate concentrations from baseline was similar between males and females.<sup>10</sup> Therefore, no further dose adjustments based on sex or other covariates evaluated are warranted.

A limitation to the simulation analysis is that all simulations and dose adjustments were only based on phosphate concentrations, whereas in clinical trials dose up-titrations, interruptions, and reductions were also based on the clinician's judgment and triggered by other safety end points as recommended in the study protocol. However, the conclusions of the comparisons between the different scenarios are expected to remain valid as the

impact of such factors would apply similarly across the simulation scenarios. Although the clinical data derived from the treatment of human patients are unpredictable and clinical trial results are necessary to determine the dosing regimens of a particular compound, the analyses presented here provide relevant tools to inform the choice of the different elements of a dose algorithm.

In conclusion, the PK-PD model provided insight to erdafitinib concentration-related phosphate changes over time and supports erdafitinib's dosing algorithm that maximizes the proportion of patients within the target phosphate range for efficacy while minimizing the proportion of patients above phosphate safety thresholds. Follow-up work linking phosphate exposure to clinical efficacy and safety end points (overall responder rate, survival, and incidence of selected adverse events)<sup>9</sup> further supports the relevance of the PD-guided dosing algorithm for erdafitinib.

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## CONFLICT OF INTEREST

A.G.D., E.V., K.S., P.D.P., A.A., A.O.H., L.Y.L., D.O., I.P., and J.J.P.R. are/were employees of Janssen Research & Development, LLC, and may hold company equity. R.F. and Q.L. were employees of SGS Exprimio NV, a paid consultant for this study.

## AUTHOR CONTRIBUTIONS

A.G.D., E.V., L.Y.L., D.O., J.J.P.R., P.D.P., A.A., A.O.H., R.F., and Q.L. wrote the manuscript. A.G.D., E.V., L.Y.L., D.O., J.J.P.R., K.S., I.P., R.F., and Q.L. designed the research. A.G.D., E.V., R.F., and Q.L. performed the research. A.G.D., E.V., L.Y.L., D.O., J.J.P.R., K.S., I.P., R.F., and Q.L. analyzed the data.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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