

Optimizing Biomarker-Based Dosing Algorithm for Erdafitinib through PK-PD Modeling and Simulations

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OBJECTIVES

- To support a phosphate-based dosing algorithm for erdafitinib, an orally administered pan-fibroblast growth factor (FGFR) tyrosine kinase inhibitor, using PK-PD modeling and simulation.
- The dosing algorithm needs to maximize erdafitinib exposure and bring most patients quickly within a predefined target phosphate range (5.5-7.0 mg/dL), while minimizing the acute phosphate toxicity-based interruptions due to serum phosphate increases above 7 mg/dL.

METHODS

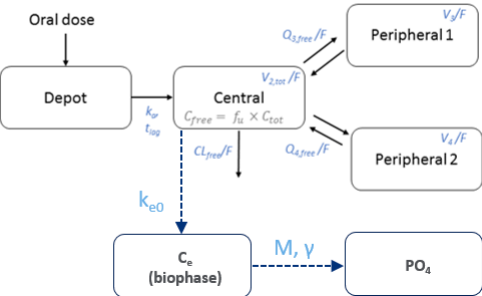
Data

- PK (total and free erdafitinib plasma concentrations) and PD (serum phosphate concentrations) data was collected in 373 subjects enrolled in six Phase 1 and Phase 2 studies. Populations included were healthy subjects and subjects with advanced solid tumors, including metastatic or unresectable urothelial cancers with FGFR genomic alterations.
- Doses investigated included single doses and once daily (QD) doses from 0.5 to 12 mg, and intermittent (7 days on/7 days off) dosing regimens of 10 and 12 mg QD. In the patient studies, dose modifications and interruptions were performed according to study guidelines based on phosphate levels targeting the 5.5-7 mg/dL range and other toxicity elements.

PK model

- A semi-mechanistic PK model, including the interaction with alpha-1-acid glycoprotein (AGP), to which erdafitinib is highly bound, was used to describe total and free erdafitinib plasma concentration profiles. Erdafitinib pharmacokinetics were described with a three-compartment linear disposition model with a first-order absorption process (**Figure 1**). The unbound fraction was related to the amount of AGP in a hyperbolic fashion, determined by the dissociation constant, Kd (**Figure 2**). It was assumed that only free drug was able to distribute and that nonlinear binding to AGP only occurred in the central compartment. Free concentrations were linked to total concentrations using the free fraction.
- Inter-individual variability (IIV) in model parameters was quantified using an exponential model for CL_{free}/F , $V_{2,tot}/F$, V_3/F and K_a . Residual unexplained variability (RUV) was additive on natural logarithmic-transformed plasma concentrations and was estimated separately for total and free erdafitinib concentrations.

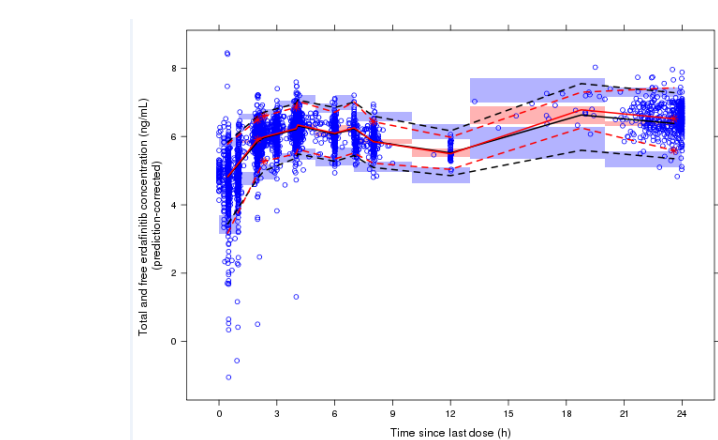
Figure 1. Schematic of the population PK-PD model for erdafitinib



t_{lag} is the lag time, k_a is the first-order absorption rate constant, CL_{int}/F is the apparent clearance of free erdafitinib, $V_{2,tot}/F$ is the apparent central volume of distribution of total erdafitinib, V_3/F and V_d/F are the apparent peripheral volumes of distribution, $Q_{12,tot}/F$ and $Q_{21,tot}/F$ are the apparent inter-compartmental clearances and f_u is the free fraction, k_{el} is the effect compartment rate constant, C_e is the free erdafitinib concentration at biophase and PO_4 are the serum phosphate concentrations.

- The presented PK model was able to capture total and free erdafitinib plasma concentration profiles (**Figure 3**). Differences in AGP binding were able to account for PK differences between healthy volunteers and patients.
- Within the range of oral doses evaluated, no evidence of concentration- and time-dependent pharmacokinetics of erdafitinib was observed.
- Following oral administration of the tablet formulation, erdafitinib is rapidly absorbed, with a mean absorption time ($1/k_a$) of 0.43 h. Erdafitinib free apparent oral clearance is 83.2 L/h, which translates into a total apparent oral clearance of 0.200 L/h for the mean free fraction observed in the target population (0.24%). The effective terminal half-life is 74.6 h. It is thus expected that after a median of 16 days, more than 95% of steady state exposure of erdafitinib is reached following once daily dosing, with approximately a 5.1-fold accumulation of erdafitinib.

Figure 3. Prediction-corrected Visual Predictive Check of the PK model for erdafitinib concentrations

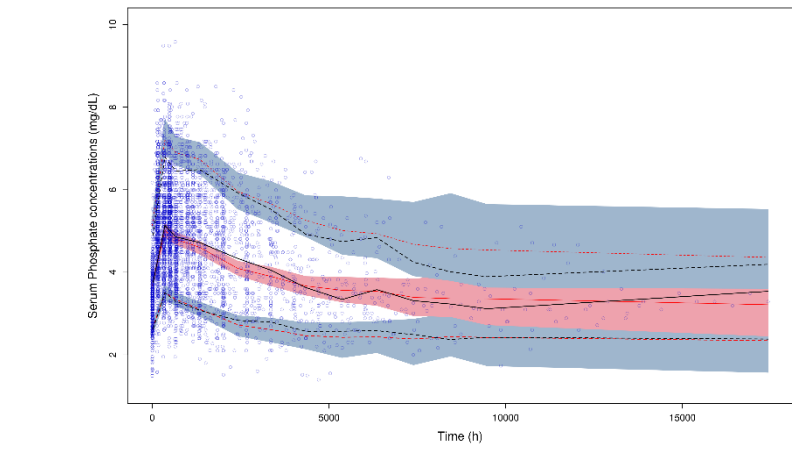


Red lines: median (solid line), 5th and 95th (dashed lines) percentiles of the simulated data with its 95% confidence interval (blue and red shaded area); black lines: median (solid line), 5th and 95th (dashed lines) percentiles of the observed data for erdafitinib.

PK-PD model

- Serum phosphate concentrations are slightly less than proportional to the free erdafitinib concentrations in a hypothetical biophase (or effect compartment). The relationship between the absolute change from baseline in serum phosphate concentrations ($\Delta[PO_4]$) and free erdafitinib plasma concentrations in the biophase was characterized by a slope model (slope M) with exponent (γ). Serum phosphate concentrations at time t ($[PO_4]_t$) were described by:
$$[PO_4]_t = [PO_4]_{BSL} + M \cdot C_e^\gamma$$
With $[PO_4]_{BSL}$ defined as serum concentration phosphate at baseline and C_e , free erdafitinib concentrations in biophase.
- In addition, an empirical function allowing phosphate concentrations to differ from their baseline value after treatment interruption was included in the model.
- An empirical function to account for an observed attenuation of phosphate concentrations over time was also implemented.
- Inter-individual variability (IIV) in model parameters was quantified using an exponential model, except for $[PO_4]_{BSL}$ for which it was additive. RUV was additive on natural logarithmic-transformed serum concentrations.
- The presented PK-PD model was able to capture longitudinal serum phosphate concentrations profiles including after interruption and discontinuation of treatment.
- Serum phosphate concentrations at baseline were 12.4% higher in females compared to males.
- Serum phosphate concentrations start rising after administration of the first dose. Following 8 mg QD dosing, maximal serum phosphate concentrations are obtained 2 weeks after starting treatment. The peak to trough fluctuation within a dosing interval is low for serum phosphate concentrations.
- The attenuation of phosphate concentrations over time was only time dependent and not concentration related. This translated into a decrease in serum phosphate concentrations with time under a constant dosing regimen.

Figure 4. Prediction-corrected Visual Predictive Check of the PK-PD model for phosphate concentrations



Red lines: median (solid line), 5th and 95th (dashed lines) percentiles of the simulated data with its 95% confidence interval (blue and red shaded area); black lines: median (solid line), 5th and 95th (dashed lines) percentiles of the observed data for phosphate concentrations.

PK and PK-PD data were analyzed using non-linear mixed effects models using the NONMEM software v7.3 aided by PsN. Simulations were performed with Simulo v7.2 Expert. Postprocessing was performed in R.

PK-PD simulations

In order to support the proposed dose adaptation rules for the final proposed erdafitinib dosing regimen (reference, **Table 1**), a number of alternative regimen were investigated (**Table 2**).

Table 1. Proposed dosing algorithm for erdafitinib (reference)

Phosphate concentration	< 5.5 mg/dL	[5.5-7] mg/dL	[7-9] mg/dL	[9-10] mg/dL	> 10 mg/dL
Dose adaptation at Day 14	9 mg QD	8 mg QD	Interruption ^a	Interruption ^a	Interruption ^a
Dose adaptation after Day 14	Same dose	Same dose	Interruption ^a Restart same dose	Interruption ^a Restart lower dose ^b	Interruption ^a Restart lower dose ^b

^a Until $PO_4 < 5.5$ mg/dL
^b Dose reduction levels: 8 mg (if up-titrated) - 6 mg - 5 mg - 4 mg - 0 mg
Phosphate measurements every week cycle 1-3, every other week cycle 4, every cycle from cycle 5 onwards. If dosing interrupted: weekly measurements.

Table 2. Investigated dosing algorithms for erdafitinib

Scenario	Starting dose	Upititration	Question to answer
Reference	8mg	at day 14, to 9mg	
Fixed dose	6mg	none	Is upititration needed?
	8mg	none	
	9mg	none	
Time of upititration	8mg	at day 28, to 9mg	Is upititration at Day 14 adequate?

RESULTS & DISCUSSION

PK-PD simulations: Reference scenario

34% of patients have phosphate levels on the 5.5-7 mg/dL target after 3 cycles (**Figure 5**). The proportion of treatment interruptions and phosphate levels above 7 mg/dL is low (**Figure 6**).

Figure 5. Proportion of patients by phosphate and dose level over time for the reference scenario

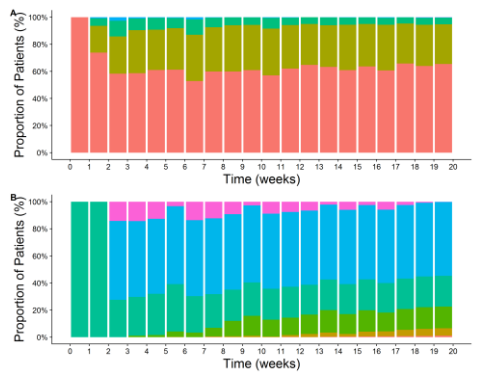
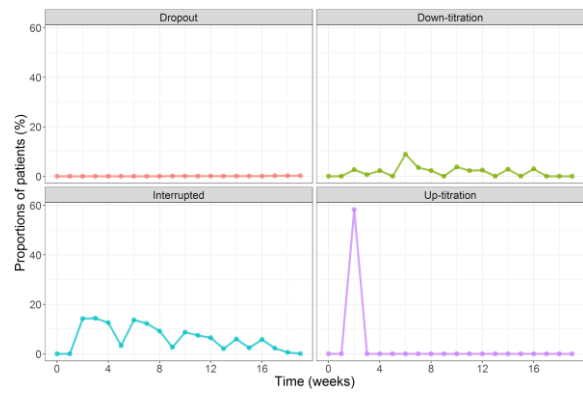


Figure 6. Proportion of patients dropped out, down-titrated, interrupted and up-titrated over time for the reference scenario



Is up-titration needed?

Not up-titrating from 8 to 9 mg at Day 14 leads to a lower dose intensity (**Figure 7**), while starting at 9 mg directly leads to a higher number of dose interruptions (**Figure 8**). The titration thus allows more patients to reach their optimum dose faster.

Figure 7. Dose intensity for the reference, 8 mg and 9 mg flat scenarios

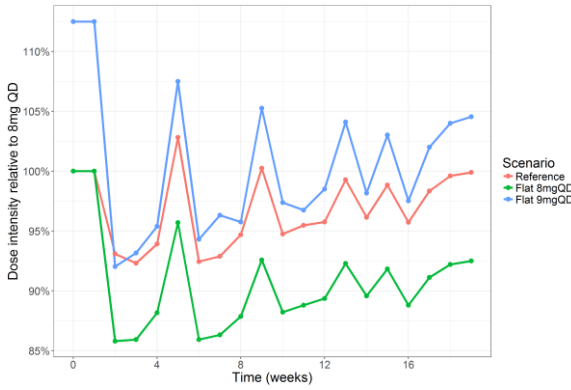
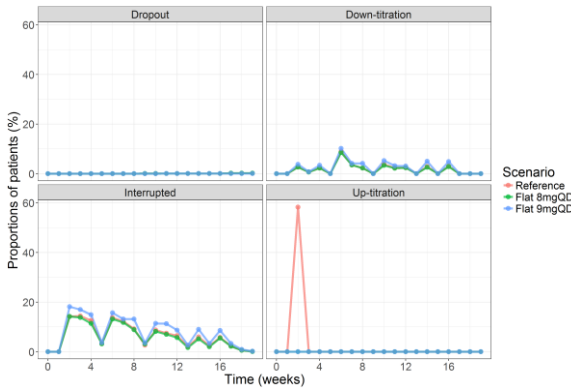


Figure 8. Proportion of interventions for the reference, 8 mg and 9 mg flat scenarios



Is up-titration at Day 14 adequate?

Titration at Day 14 vs. Day 28 leads to slightly higher dose intensity, thus more patients exposed faster to a higher dose (**Figure 9**) without increasing the number of interruptions (**Figure 10**). Phosphate levels at Day 14 are thus an adequate endpoint to guide individualized dosing for erdafitinib.

Figure 9. Dose intensity for the up-titration at Day 14 and at Day 28

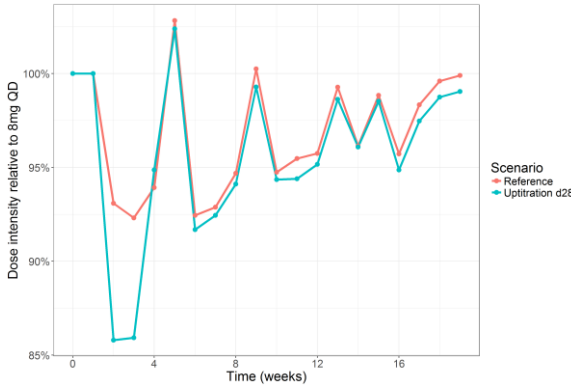
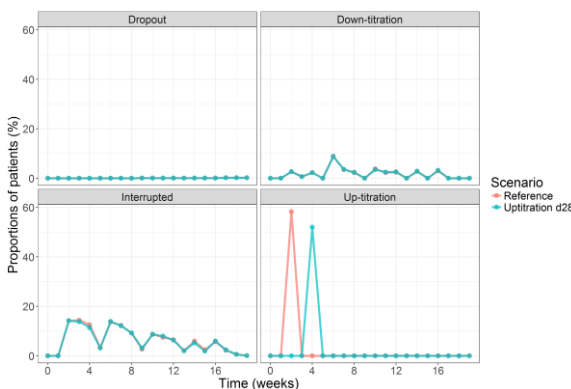


Figure 10. Proportion of interventions for the up-titration at Day 14 and at Day 28



CONCLUSION

- The PKPD modelling and simulation approach developed was used to support an individualized, phosphate-based dosing algorithm in an ongoing Phase 2 study.
- The PK-PD simulation model was used to further refine the phosphate thresholds in the dosing algorithm for the Phase 3 study.

Investigational compound Erdafitinib (JNJ42756493) was discovered in collaboration with Astex Pharmaceuticals.