# Development and evaluation of a predictive model of hyperphosphatemia induced by inhibition of FGFR by extending an existing multiscale systems pharmacology

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## Abstract

**OBJECTIVES:** Fibroblast growth factor receptor (FGFR) inhibition has been investigated as a potential target for treating cancer. Hyperphosphatemia (HP) has been observed clinically following FGFR inhibition due to its role in regulating phosphate (P) balance through FGF23, which regulates urinary P excretion and indirectly impacts dietary P absorption and calcitriol (C) activation. **An existing systems pharmacology model was leveraged to explore whether HP circumvention can be achieved via intermittent dosing and concomitant P binders following administration of ASP5878, an FGFR inhibitor investigated for treatment of solid tumors (NCT02038673).**

**METHODS:** A systems pharmacology model (Bone, 2010) was extended to describe changes in serum P, C, parathyroid hormone (PTH), and FGF23 following oral ASP5878 administration. The model evaluated concomitant P binder and impact of varied dosing regimens on exposure-related P changes. Analyses were conducted in R; simulation and estimation included mrgsolve and minqa. QD and BID ASP5878 dosing, total daily dose, and intermittent, 5 days on / 2 off, and 4 days on / 3 off, regimens were considered.

**RESULTS:** ASP5878 PK followed a 1 compartment model (typical $t1/2 = 2.63$h). **Added mathematical descriptions included: FGF23 control urinary P, PTH and C production, with feedback on FGF23 production from P and C. P binder was estimated to decrease its dietary bioavailability by up to 32%.** The extended model described the time-course and magnitude of dose-related increases observed for P, C, FGF23 and PTH, including P > 6 mg/dL at doses ≥ 32 mg/day. P binder was predicted to mildly alleviate the increase at targeted doses. Efficacious response was not obtained by any simulated regimen that minimized to acceptable P.

**CONCLUSIONS:** Results from the extended systems model supported program termination.

## Methods

1. Systems pharmacology model [1] extension with population PK for exposure-response on serum phopshate, calcium, parathyroid hormone (PTH), and FGF23 following oral ASP5878 administration. See QR code for further details.
2. Evaluated concomitant P binder and impact of varied dosing regimens on exposure-related P changes.
3. Population PK model development in NONMEM®. All other analyses were conducted in `R` [2]; simulation and estimation included `mrgsolve` [3] and `minqa` [4].
4. Simulations:
   - Can dose-adjustments, with or without P-binder, avoid hyperphosphatemia? (See QR code)
   - Simulation scenarios: QD and BID ASP5878 dosing, total daily dose, and intermittent, 5 days on / 2 off, and 4 days on / 3 off; with and without P-binder. *Figure 5*

## Conclusion

- Extension of systems pharmacology model allowed for characterization of FGFR inhibition on multiple physiologically-based homeostatic mechanisms for phosphate balance.
- The impact of phosphate binder concomitant treatment could also be integrated into the systems model.
- Serum phosphate response to FGFR inhibitor therapy was associated with drug exposure and the magnitude and time-course of these changes was predicted to be influenced by the dosing regimen.

**Results from the extended systems model supported program termination.**

## References

[1] Peterson, M.C. and Riggs, M.M. A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. *Bone* **46** (2010):49–63.

[2] R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria (2014). URL `http://www.R-project.org/`

[3] Baron, K.T., Hindmarsh, A.C., Petzold, L.R., Gillespie, B. and Margossian, C. mrgsolve: Simulation from ode-based population pk/pd and systems pharmacology models. Technical report, Metrum Research Group LLC, http://metrumrg.com/opensourcetools.html (2016 R package version 0.6.0).

[4] Bates, D., Mullen, K.M., Nash, J.C. and Varadhan, R. *minqa: Derivative-free optimization algorithms by quadratic approximation* (2014). R package version 1.2.4. URL `https://CRAN.R-project.org/package=minqa`

## Results

### Model Modifications and Extensions

**Existing Published Model was Expanded**

- The model now includes a predictive population PK for ASP5878 and integrates FGFR/FGF23 regulation of phosphate into the existing QSP model.
- These extensions were expressed through ordinary differential equations (QR code: equations, PK parameters and new system model parameters).
- FGFR-related effects exist in kidneys (Vitamin D regulation and phosphate excretion), in PT gland (PTH release), and in the gut (phosphate bioavailability indirectly through Vitamin D changes).

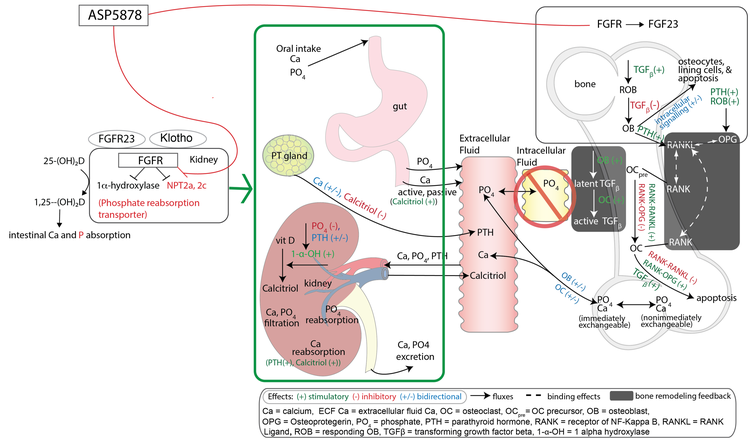


Figure 1: *Multiscale physiologic model; reproduced from Peterson and Riggs[1] with proposed modifications and extensions noted.*

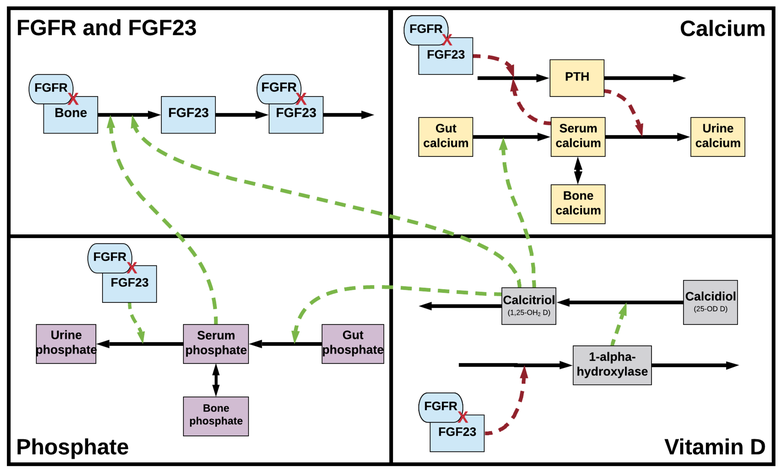


Figure 2: *Extensions to describe FGFR/FGF23 control of phosphate homeostasis.*

### Model Fits

**Model Predictions Compared with Observed Data: Phosphate**

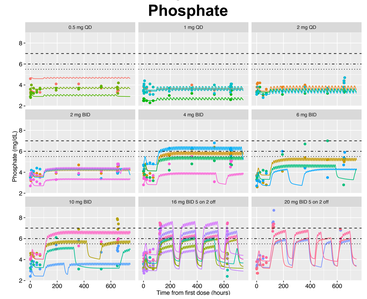


Figure 3: *Phosphate by regimen; reference lines at 5.5, 6 and 7 mg/dL*

**Model Predictions Compared with Observed Data: Calcitriol**

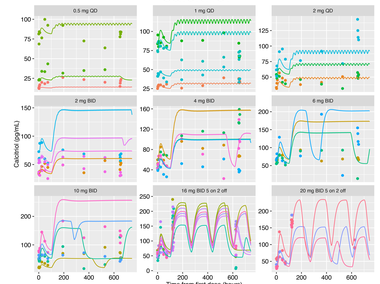


Figure 4: *Calcitriol by regimen*

**Symbols = Clinical Observations; Lines = Individualized Model Predictions.**

### Simulations

**Model Predictions Across Dosing Regimens + Effect of Phosphate Binder Intervention**

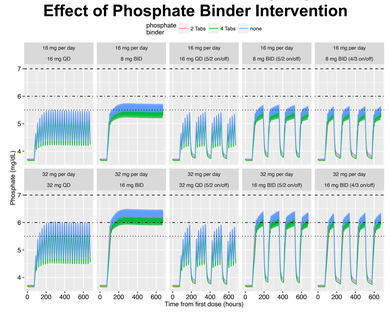


Figure 5: *Simulated phosphate response for candidate regimens with and without phosphate binder effect*

### Model Code and Additional Supporting Information

This study was funded by Astellas Pharma, Inc.