Poster Supplement

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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1 Additional Tables and Figures

Table 1: Population PK estimates.

			Estimate	95% CI	% RSE
Structural model parameters					
CL/F (L/h)	$\exp(\theta_1)$	Apparent oral clearance	25.2	23.0, 27.5	4.61
V/F (L)	$\exp(\theta_2)$	Apparent oral volume of distribution	95.5	84.0, 107	6.11
Ka (1/h)	$\exp(\theta_3)$	Oral absorption rate constant	4.21	2.70, 5.73	18.4
D1 (h)	$\exp(\theta_4)$	Oral dose duration	0.640	0.442, 0.838	15.8
Interindividual variance parameters					
IIV-CL/F	$\Omega_{1,1}$	Variance of CL	0.0797 [CV%=28.8]	0.0337, 0.126	29.4
IIV-V/F	$\Omega_{2,2}$	Variance of V/F	0.0832 [CV%=29.5]	0.0442, 0.122	23.9
IIV-Ka	$\Omega_{3,3}$	Variance of Ka	1.07 [CV%=138]	0.344, 1.79	34.6
IIV-D1	$\Omega_{4,4}$	Variance of D1	0.766 [CV%=107]	0.390, 1.14	25
Interindividual covariance parameters					
V/F-CL/F	$\Omega_{2,1}$	Covariance of V/F-CL/F	0.0606	0.0193, 0.102	34.8
Ka-CL/F	$\Omega_{3,1}$	Covariance of Ka-CL/F	-0.0233	-0.124, 0.0776	221
Ka-V/F	$\Omega_{3,2}$	Covariance of Ka-V/F	-0.0669	-0.187, 0.0530	91.4
D1-CL/F	$\Omega_{4,1}$	Covariance of D1-CL/F	0.0459	-0.0348, 0.127	89.7
D1-V/F	$\Omega_{4,2}$	Covariance of D1-V/F	0.0487	-0.0304, 0.128	82.9
D1-Ka	$\Omega_{4,3}$	Covariance of D1-Ka	-0.00400	-0.308, 0.300	3870
Residual variance					
Proportional	$\Sigma_{1,1}$	Variance	0.158 [CV%=39.7]	0.113, 0.203	14.5
Additive	$\Sigma_{2,2}$	Variance	0.0265	0.0191, 0.0339	14.2

Abbreviations: CI = confidence intervals; CV = coefficient of variation; SD = standard deviation; SE = standard error; RSE = Residual standard error
Confidence intervals = estimate ± 1.96 * SE
CV% of omegas = sqrt(exp(estimate) - 1) * 100
CV% of sigma = sqrt(estimate) * 100
Source code: paramTable.R
Source file: PK_paramTable.tex

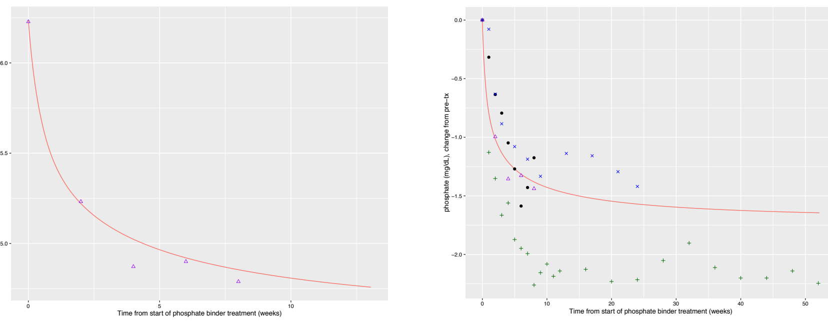
The first five additional system model parameters (Table 2), ("ctriolSTIMpoMax","FGFRIC50renal","kFGF23", "FGFRrenalMAX", "FGF23IC50vitD") were optimized using the `newoua` sum of squares minimization using clinical phosphate and calcitriol data. Remaining parameters were first tuned based on graphical evaluations relative to the observed data (phosphate, calcitriol, PTH, FGF23, and calcium).

Table 2: Additional system model parameters.

Parameter	Estimate
ctriolSTIMpoMax	18.2
FGFRIC50renal	15.1
kFGF23	0.187
FGFRrenalMAX	0.533
FGF23IC50vitD	18.6
FGF23IC50	6.00
ctriolSTIMgam	0.600
phosSTIMfgf23Gam	1.00
htrMTT	3.00
T71	0.0100
FGFRIC50bone	0.300
FGFRboneMAX	0.900
phosFctriol	2.00
koutRPHOS	0.0200
FGF23STIMMAX	1.00
FGF23STIMMAXvitD	4.00
kFGF	0.0800

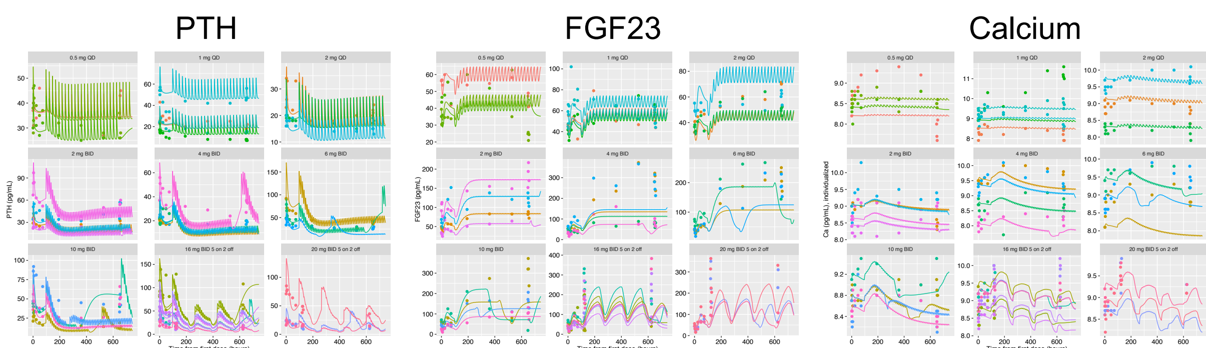
Phosphate Binder Effect

- Simulate Chronic Kidney Disease: GFR decreased to mimic severe renal disease ➔ phosphate increases and secondary hyperparathyroidism.
- Evaluate effect of phosphate binder (decreased phosphate bioavailability) on serum phosphate concentrations, compare with clinical data



Nephrology, Dialysis, Transplantation 25 (11): 3707-17 (x); Renvela (sevelamer carbonate) Prescribing Information (+); Kidney International 67 (95): S13-20 (o)

Model Predictions Compared with Observed Data: Other Markers



2 Equations included in the model modifications and extensions

Equations related to the *FGFR and FGF23* panel in the poster Figure 2.

$$\mathrm{dxdt\_FGF23} = \mathrm{JFGF23} \times \mathrm{FGFRINHbone} \times \mathrm{PhosSTIM} \times \mathrm{FTR} - \mathrm{kFGF} \times \mathrm{FGF23} \times \mathrm{FGFRbone} \tag{1}$$

$$\mathrm{dxdt\_FGFRbone} = \mathrm{kFGF} \times \mathrm{FGFRINHbone} - \mathrm{kFGF} \times \mathrm{FGFRbone} \tag{2}$$

$$\mathrm{JFGF23} = \mathrm{BFGF23} \times \mathrm{kFGF} \tag{3}$$

$$\mathrm{FGFRINHbone} = 1.0 - \left(\frac{(\mathrm{FGFRboneMAX} \times \mathrm{CP5878})}{(\mathrm{CP5878} + \mathrm{FGFRIC50bone})} \right) \tag{4}$$

$$\begin{aligned} \mathrm{VDratio} &= B / B_0 \\ \mathrm{VDnull} &= \mathrm{VDratio} - 1.0 \\ \mathrm{if}(\mathrm{VDratio} < 1.0)\ \mathrm{VDnull} &= 0.0 \\ \mathrm{ctriolSTIM} &= 1.0 + \mathrm{VDnull} \times \frac{\mathrm{ctriolSTIMmax}}{(\mathrm{VDnull} + \mathrm{ctriolSTIMec50})} \end{aligned} \tag{5}$$

FTR is transit model driven by calcitriol

$$\begin{aligned} \mathrm{ftrKtr} &= \frac{(1+3)}{\mathrm{ftrMTT}} \\ \mathrm{dxdt\_FTR1} &= \mathrm{ftrKtr} \times \left(\frac{\mathrm{C8}}{\mathrm{Calcitriol0}} \right) - \mathrm{FTR1} \times \mathrm{ftrKtr} \\ \mathrm{dxdt\_FTR2} &= \mathrm{ftrKtr} \times (\mathrm{FTR1} - \mathrm{FTR2}) \\ \mathrm{dxdt\_FTR3} &= \mathrm{ftrKtr} \times (\mathrm{FTR2} - \mathrm{FTR3}) \\ \mathrm{dxdt\_FTR} &= \mathrm{ftrKtr} \times \mathrm{FTR3} - \mathrm{ftrKtr} \times \mathrm{FTR} \end{aligned} \tag{6}$$

Equations related to the *Vitamin D* panel in the poster Figure 2.

Previous: $\mathrm{SE} = \mathrm{T65} \times \mathrm{T68} \times \mathrm{PhosEffect}$
Updated: $\mathrm{SE} = \mathrm{T65} \times \mathrm{T68} \times \mathrm{HTR}$

$$\mathrm{dxdt\_AOH} = \mathrm{SE} - \mathrm{T64} \times \mathrm{AOH} \tag{7}$$

$$\mathrm{htrKtr} = (1+8)/\mathrm{htrMTT} \tag{8}$$

$$\begin{aligned}
\mathrm{dxdt_HTR1} &= \mathrm{htrKtr} \times \mathrm{FGF23STIMvitD} - \mathrm{HTR1} \times \mathrm{htrKtr} \\
\mathrm{dxdt_HTR2} &= \mathrm{htrKtr} \times (\mathrm{HTR1} - \mathrm{HTR2}) \\
\ldots \mathrm{dxdt_HTR}(3\ldots7) &= \mathrm{htrKtr} \times (\mathrm{HTRn} - 1 - \mathrm{HTRn}) \\
\mathrm{dxdt_HTR8} &= \mathrm{htrKtr} \times (\mathrm{HTR7} - \mathrm{HTR8}) \\
\mathrm{dxdt_HTR} &= \mathrm{htrKtr} \times \mathrm{HTR8} - \mathrm{htrKtr} \times \mathrm{HTR}
\end{aligned} \tag{9}$$

$$\mathrm{FGF23STIMvitD} = 1.0 + \left(\mathrm{FGF23STIMMAXvitD} \times \frac{\mathrm{CP5878}}{(\mathrm{CP5878} + \mathrm{FGF23IC50vitD})}\right) \tag{10}$$

Equations related to the *Calcium* panel in the poster Figure 2.

Previous: $\mathrm{EPTH} = \mathrm{T63} \times \mathrm{FCTD}$
Updated: $\mathrm{EPTH} = \mathrm{T63} \times \mathrm{FCTD} \times \mathrm{FGF23STIM}$

$$\mathrm{FGF23STIM} = 1.0 + \left(\mathrm{FGF23STIMMAX} \times \frac{\mathrm{CP5878}}{(\mathrm{CP5878} + \mathrm{FGF23IC50})}\right) \tag{11}$$

Equations related to the *Phosphate* panel in the poster Figure 2.

Previous: $\mathrm{dxdt\_ECCPhos} = \mathrm{J41} - \mathrm{J42} - \mathrm{J48} + \mathrm{J53} - \mathrm{J54} + \mathrm{J56}$
Updated: $\mathrm{dxdt\_ECCPhos} = \mathrm{J41} - \mathrm{J42} - \mathrm{J48} + \mathrm{J53}$

Phosphate oral absorption
Previous: J53 = T52 × PhosGut
Updated: J53 = T52 × PhosGut × RPHOS

$$\mathrm{dxdt\_PhosGut} = \mathrm{OralPhos} \times \mathrm{F12} \times \mathrm{RPHOS} - \mathrm{J53}; \tag{12}$$

Phosphate renal excretion
J48 = (((0.88 × GFR × C2 × FGFR) - T47))

$$\mathrm{dxdt\_FGFR} = \mathrm{kFGF23} \times \mathrm{FGFRINH} - \mathrm{kFGF23} \times \mathrm{FGFR} \tag{13}$$

$$\mathrm{FGFRINH} = 1.0 - \left(\frac{(\mathrm{FGFRrenalMAX} \times \mathrm{CP5878})}{(\mathrm{CP5878} + \mathrm{FGFRIC50renal})}\right) \tag{14}$$

Calcitriol-dependent PO4 absorption from:

$$\mathrm{ctriolSTIMpoEC50} = \mathrm{Calcitriol0} \times (\mathrm{ctriolSTIMpoMax} - 1) \tag{15}$$

$$\mathrm{ctriolSTIMpo} = \mathrm{C8} \times \frac{\mathrm{ctriolSTIMpoMax}}{(\mathrm{C8} + \mathrm{ctriolSTIMpoEC50})} \tag{16}$$

$$\mathrm{dxdt\_RPHOS} = \mathrm{koutRPHOS} \times \mathrm{ctriolSTIMpo} - \mathrm{koutRPHOS} \times \mathrm{RPHOS} \tag{17}$$

3 Reproducible Code

The model code is provided in the **asp5878_SysPcolModel.cpp** file and the code to run it is provided in the **SimulateRegimens.R** script. Note that the R script assumes both .cpp file and the .R file are located in the same directory.