Quantitative Systems Pharmacology Modeling of X-linked Hypophosphatemia Disease Pathway Normalization to Predict the Impact of Burosumab Treatment on Serum Biomarkers in Adult and Pediatric Patients

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BACKGROUND

- XLH is a rare genetic musculoskeletal disease caused by excess serum levels of FGF23, which regulates serum phosphate, resulting in hypophosphatemia[1,2]
- Burosumab, a monoclonal antibody targeting FGF23, is approved for the treatment of adult and pediatric patients with XLH in the US and other countries[3,4]
- Burosumab normalizes serum hypophosphatemia in XLH patients by targeting excess FGF23, allowing increased phosphate reabsorption in the kidney and production of vitamin D[3]
- Both hypo- and hyperphosphatemia can result in serious pathological effects; therefore, after beginning treatment with burosumab, serum phosphate levels must be monitored until a dose is achieved that normalizes serum phosphate[3]
- A QSP model of integrated calcium homeostasis and bone biology was constructed by Peterson and Riggs to describe a broad range of clinical and therapeutic conditions,[5] and has been built upon and utilized to assess various drugs and indications[6,7]

STUDY OBJECTIVE

- To extend a QSP model by incorporating XLH disease mechanisms and burosumab impact on serum phosphate and other biomarkers in adult and pediatric patients with XLH

METHODS

- The base model was revised to include the pathophysiology associated with the XLH disease state based on data obtained from 28, 22, and 15 patients with XLH in studies KRN23-INT-001, KRN23-INT-002, and KRN23-003 (NCT01340482, NCT01571596, and NCT03233126), respectively (**Table 1**)

Table 1. Clinical Trial Summary

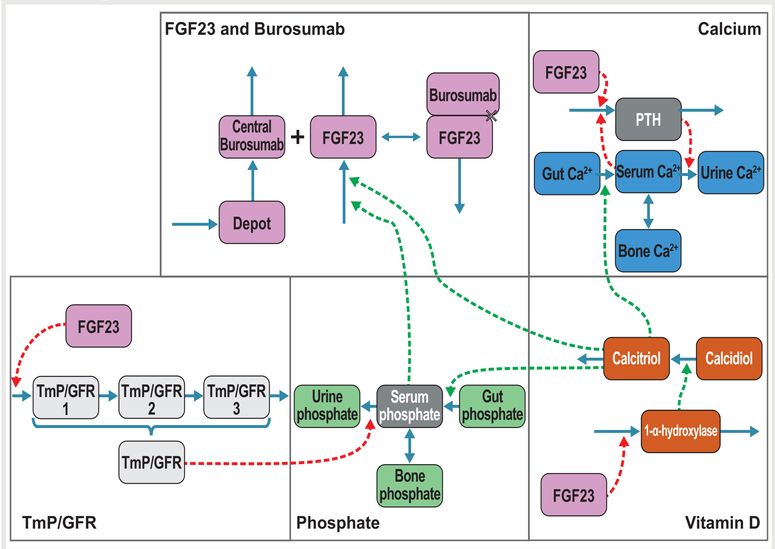
Study	XLH population	N	Phase	Dose regimen	Dose levels
NCT01340482	Adult	28	1/2	Multiple doses (Q4W for 4 months)	0.05, 0.10, 0.30, 0.60 mg/kg
NCT01571596	Adult	22	1/2	Multiple doses (Q4W for 88 weeks)	0.05, 0.10, 0.30, 0.60, 1.0 mg/kg
NCT03233126	Pediatric	15	3	Multiple doses (Q2W for 40 weeks)	0.8 mg/kg initial, escalated up to 1.2 mg/kg

- The following changes were considered for patients with XLH:
  - Serum burosumab concentrations for clinical studies were estimated using a maximum posterior Bayesian method, with fixed and random effects derived from a one-compartment PK model
  - Serum burosumab concentrations were linked to a TMDD model that includes FGF23 binding and elimination of the FGF23-burosumab complex
  - FGF23 inversely controls the expression level of the renal tubular transporters (Npt2a and Npt2c) involved in phosphate reabsorption. Thus, FGF23 impacts TmP/GFR. To describe the effect between FGF23 signaling and TmP/GFR modulation, a transit compartment model was incorporated
  - A physiologically based mathematical model of FGF23-mediated control was implemented to match any differences in baseline and change of serum phosphate, PTH, active vitamin D (calcitriol), calcium, or TmP/GFR
  - When focusing on the pediatric XLH patient population, the model established for adult XLH patients was scaled to account for differences observed in baseline values between adult and pediatric XLH patients, as well as for typical differences in physiology between adults and pediatrics (regardless of disease status)
- Model calibration and evaluation were conducted by comparing summary plots to obtained data

RESULTS

- The base QSP model was updated to include XLH disease mechanisms and burosumab dynamics, including the binding of serum burosumab to the FGF23 target (**Figure 1**). Feedback mechanisms already included in the QSP model were used to predict changes in serum phosphate and other biomarkers
- The following changes were implemented into the model:
  - FGF23 production rate was updated to be greater in patients with XLH than healthy individuals, and were set such that FGF23 was at steady state in patients with XLH. The FGF23 production rate was estimated based on individual baseline FGF23 levels, and the FGF23 degradation rate constant was derived from the literature
  - A quasi-steady state TMDD model was incorporated by optimizing the kinetic parameters for FGF23-burosumab binding (KD, Kint, Kon)
  - The transit compartment model was implemented to be doubled TmP/GFR within a burosumab dosing interval when predicted unbound FGF23 decreased to 35% and 45% of baseline for XLH in adult and pediatric patients, respectively
  - The predicted phosphate median baseline for adults with XLH was lower than the observed by approximately 0.4 mg/dL. This phosphate baseline was adjusted by increasing the input flux of phosphate into the systemic circulatory system by a factor of 5
  - Patients with XLH did not appear to experience marked shifts in PTH gland capacity. Removal of the expressions allowing for expansion or contraction of the parathyroid gland pool capacity did not impact the model fit and resulted in improved model stability
  - Scaling factors were implemented to adjust the PTH and calcium baselines to match those in adults and pediatrics with XLH

Figure 1. Base QSP Model Including the FGFR and FGF23 Pathway



Adapted from Riggs MM et al 2020.[7]
Gray boxes indicate parameters modified for the XLH model.

- The updates resulted in a model that can reproduce the time-concentration profiles of serum phosphate, along with total FGF23, TmP/GFR, and active vitamin D of the XLH adult patient consistently. The bone QSP model for XLH was successfully optimized to account for new information
- The final QSP model described patient-level data well for changes in PK and PD biomarkers; simulations recapitulated results from the burosumab studies (**Figures 2–5**)

Figure 2. Predicted and Observed Burosumab Concentration Over Time

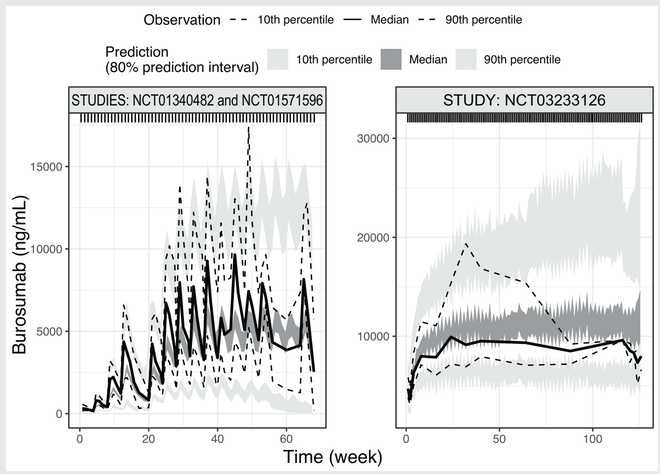


Figure 3. Predicted and Observed Total FGF23 Concentration Over Time

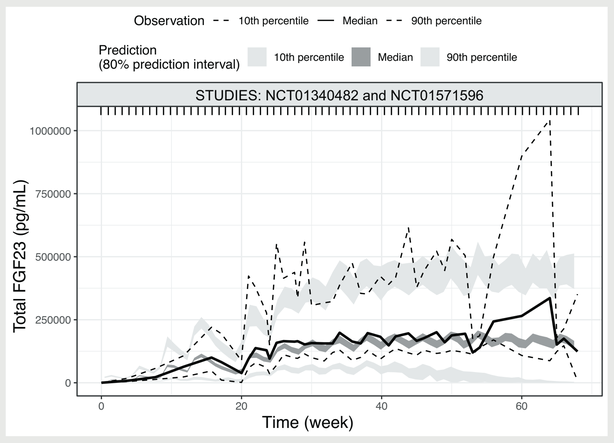


Figure 4. Predicted and Observed TmP/GFR Over Time

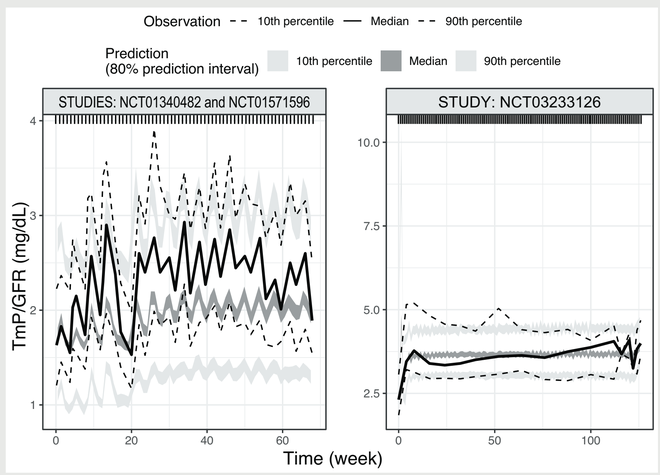
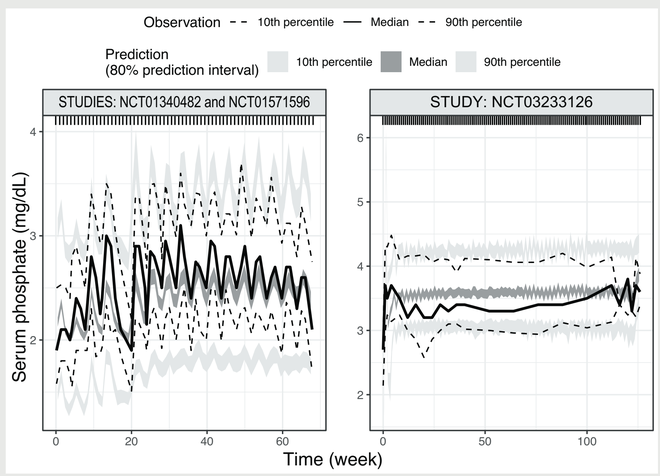


Figure 5. Predicted and Observed Serum Phosphate Concentration Over Time



CONCLUSIONS

- The XLH QSP model reproduced clinically observed changes in pharmacodynamic markers in both adult and pediatric patients with XLH
- Normalization of serum phosphate with burosumab treatment was successfully replicated, facilitating a better understanding of burosumab dosing in patients with XLH going forward
- The model could potentially be used to optimize treatment in the clinical setting

ABBREVIATIONS

FGF23, fibroblast growth factor 23; FGFR, fibroblast growth factor receptor; PD, pharmacodynamic; *PHEX*, phosphate-regulating endopeptidase homolog X-linked; PK, pharmacokinetic; PTH, parathyroid hormone; Q(2, 4)W, every (2, 4) weeks; QSP, quantitative systems pharmacology; TMDD, target-mediated drug disposition; TmP/GFR, the ratio of tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR); XLH, X-linked hypophosphatemia.

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