

# Development of a Quantitative Systems Pharmacology Model to Support Dosing of rhPTH(1-84), a Recombinant Human Parathyroid Hormone, in Adult Patients with Hypoparathyroidism

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## BACKGROUND

rhPTH(1-84), a full-length Recombinant Human Parathyroid Hormone, is approved in the US and Europe as an adjunct to calcium and active vitamin D to control hypocalcemia in patients with chronic hypoparathyroidism (hypoPT). rhPTH(1-84) is indicated for once daily (QD) dosing, and the dose is to be individualized to achieve a serum calcium level in the lower half of the normal range (target range).

A quantitative systems pharmacology (QSP) model of integrated calcium homeostasis and bone remodeling[1] was originally adapted for patients with hypoPT by including

1. the concentration-time profiles of PTH,
2. oral intake of calcium and active vitamin D, and
3. by performing various adjustments on the parathyroid gland pool and the ability of the gland to grow in size and in capacity for secretion.

## OBJECTIVE

The objectives of this project were to

1. enhance a QSP model by integrating additional drug- and disease-specific components to further improve the predictive performance of the model, and
2. perform simulations to ultimately predict the effects of QD and twice daily (BID) administrations of rhPTH(1-84) on serum calcium and urinary calcium excretion in adult patients with hypoPT.

## METHODS

As part of the original QSP model development, the following changes were applied to improve the predictive performance of the model:

1. implementation of calcium oral intake component,
2. implementation of calcitriol oral intake component,
3. model adjustment to describe the PTH concentrations, parathyroid gland pool and the ability of the gland to grow in size and in secretion capacity.

Additional drug- and disease-specific components were integrated into the QSP model, and the model was re-qualified using accumulated PK/PD data in hypoPT patients.

Simulations were performed with the enhanced QSP model to predict the following PK and PD endpoints for various QD and BID doses of rhPTH(1-84) and standard of care (SOC, calcium supplement + active vitamin D):

1. Concentration-time profiles of PTH,
2. Serum calcium,
3. Urinary calcium excretion, and
4. Probability of hypercalciuria (defined as 24-h urinary calcium above the normal range (i.e., >7.5mmol (300mg) in males and >6.25mmol (250mg) in females)

The final QSP was ported to the R package "mrgsolve".

## RESULTS

### Baseline Characteristics and Populations

A total of 135 adult patients with hypoPT in five clinical studies including subcutaneous (SC) administration of QD (25, 50, 100 µg) and BID (25 or 50 µg) regimens were included in the analysis, characterized by:

- 110 (81%) female and 25 (19%) male subjects with hypoPT.
- 53 (39.3%) post-menopausal women and 57 (42.2%) pre-menopausal women.
- Median (range) age and body weight in the population were 48.0 years (19.0 – 75.0) and 83.4 kg (47.8 – 177), respectively.

### Exploratory PK and PD Data Analysis

Based on exploratory analyses, the following were observed:

- Peak concentrations of PTH increased with higher dose levels. Subjects presented a first peak of PTH within 5 to 30 min, a smaller peak at 1 to 2 hours. The model was customized to take into account the double absorption peak profiles of PTH).
- The original QSP model under-predicted urinary calcium and therefore the probability of hypercalciuria.

## RESULTS – MODEL OPTIMIZATION

### Model Customization #1: Absorption of PTH

A population PK analysis was performed to assess the subject-specific rate of absorption of PTH. The absorption model was customized to allow an optimal description of subjects with single or double absorption peaks.

- A total of 68.0% of subjects were modeled using a double absorption process whereas 32% of subjects were modeled using a single absorption process.
- For subjects with a double absorption process, 62.9% of the dose was used to describe the first peak, while 37.1% was used to describe the second peak, with a lag time of 0.98 h.
- The rate constant of absorption was 0.211 with a between-subjects variability (BSV) of 76.5%. Subject-level  $K_a$  values (i.e., posthoc values derived with the population PK model) were implemented in the QSP.

### Model Customization #2: Calcium Reabsorption

Various publications have reported a lower renal reabsorption of calcium in patients with hypoPT.[2] The effect is believed to be due to lower number of sites of hormone action in renal tubules, where it promotes calcium reabsorption. Based on this mechanism of action, the QSP model was customized as follows:

$$CaReabsActive = \frac{CaReabs_{max} \times Ca_{serum} \times PTH_{effect}}{CaReabs_{50} + Ca_{serum}}$$

$$PTH_{effect} = \frac{PTH_{effect_{max}} \times PTH_{plasma}}{PTH_{effect_{50}} + PTH_{plasma}}$$

Where  $CaReabs_{50}$  = Caserum needed to achieve 50% of  $CaReabs_{max}$ ;  $CaReabsActive$  = rate of calcium active renal reabsorption (mmol/h);  $CaReabs_{max}$  = maximum  $CaReabsActive$ ; Caserum = Calcium serum concentration (mM) (T16 in model code);  $PTH_{plasma}$  = PTH plasma concentration (pM);  $PTH_{effect}$  = effect of PTH on Calcium renal active reabsorption (unitless);  $PTH_{effect_{50}}$  =  $PTH_{plasma}$  needed to achieve 50% of  $PTH_{effect_{max}}$  (T17 in model code);  $PTH_{effect_{max}}$  = maximum  $PTH_{effect}$ .

In the original QSP model, the maximum effect of PTH on calcium renal active reabsorption,  $PTH_{effect_{max}}$ , was fixed to 1.06147 (106% of reference reabsorption) and the PTH concentration needed to achieve 50%  $PTH_{effect_{max}}$  was scaled. In the current QSP model, the following values were used:

$$PTH_{effect_{50}} = 3.85 \times T16 - 3.85 = 0.2366595$$

### QSP Model Qualification

The enhanced QSP model presented an adequate predictive performance of plasma PTH central tendency (population estimates), in serum calcium and urinary calcium excretion, however, underestimated variability (Figure 1 and Figure 2).

Figure 1. QSP Model Qualification - Study SHP634-101<sup>[3]</sup>

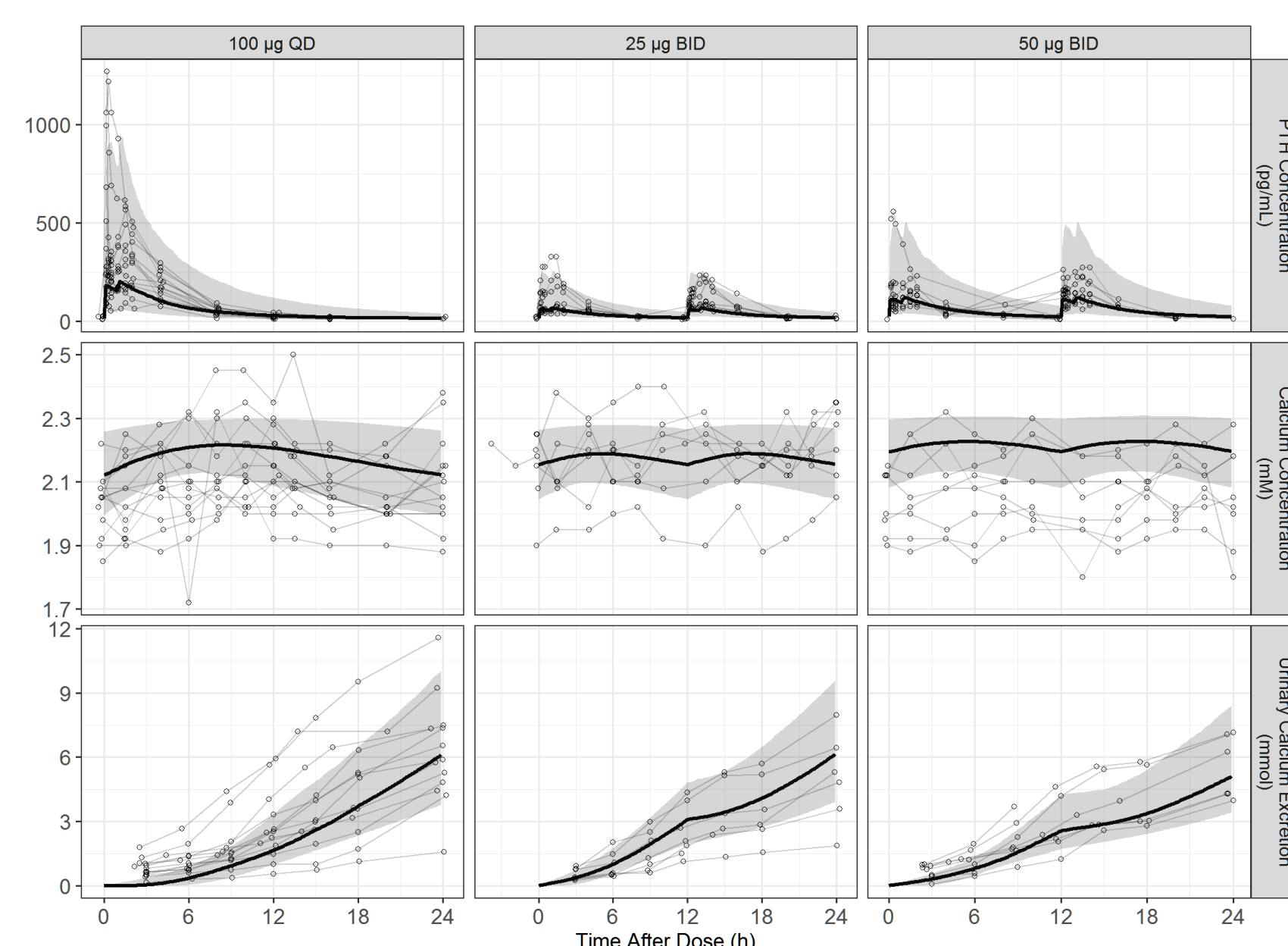
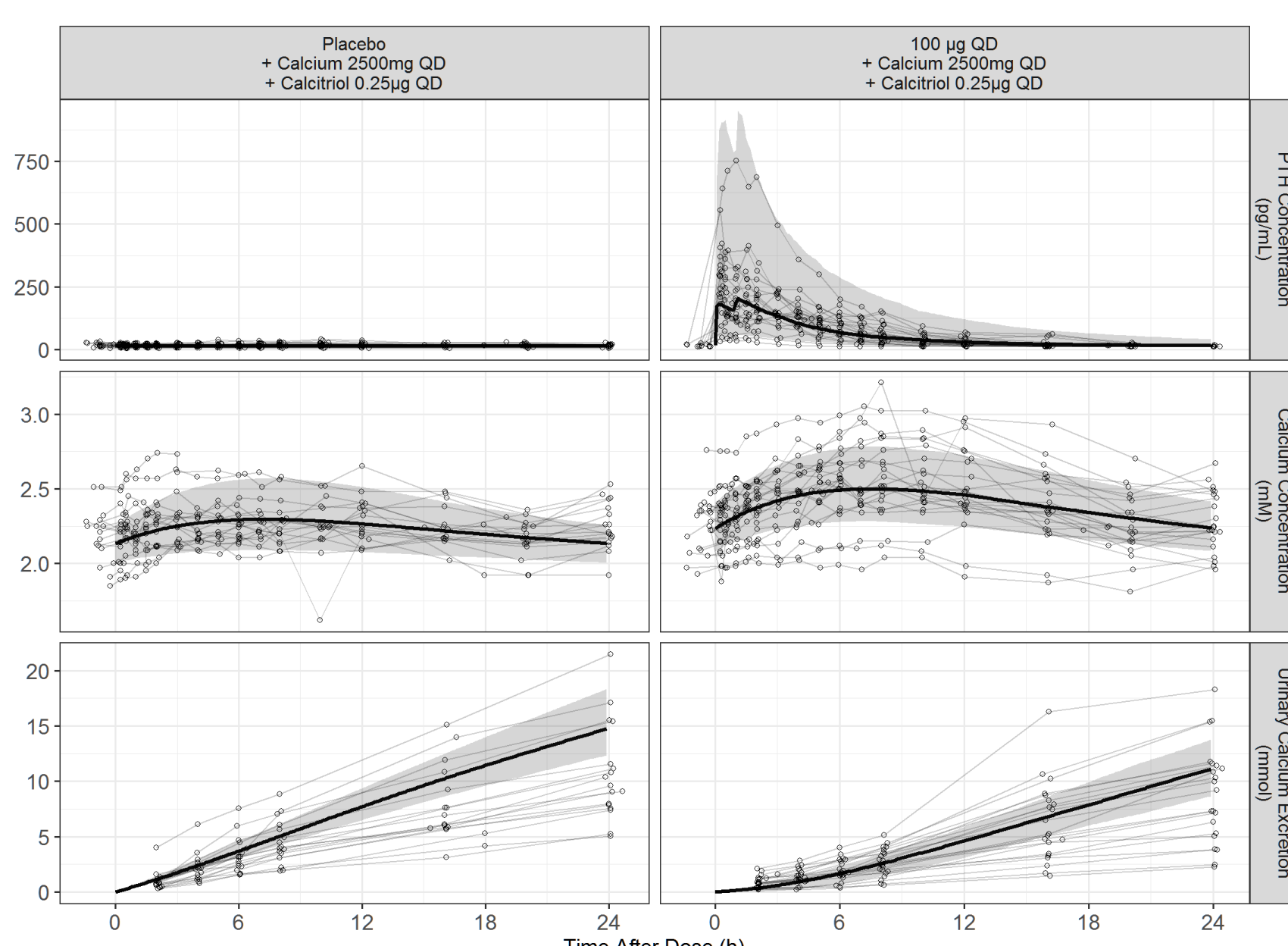


Figure 2. QSP Model Qualification - Study Mosekilde-IIT<sup>[4]</sup>



## RESULTS - SIMULATIONS

### Application of QSP Model

The final QSP model was used to predict PK and PD of rhPTH(1-84) in patients with partial PTH production (endogenous PTH levels ranging from 5.63 to 27.2 ng/mL). Simulation results are presented in Figure 3 and Figure 4.

Figure 3. Simulations (100 µg Total Daily Dose)

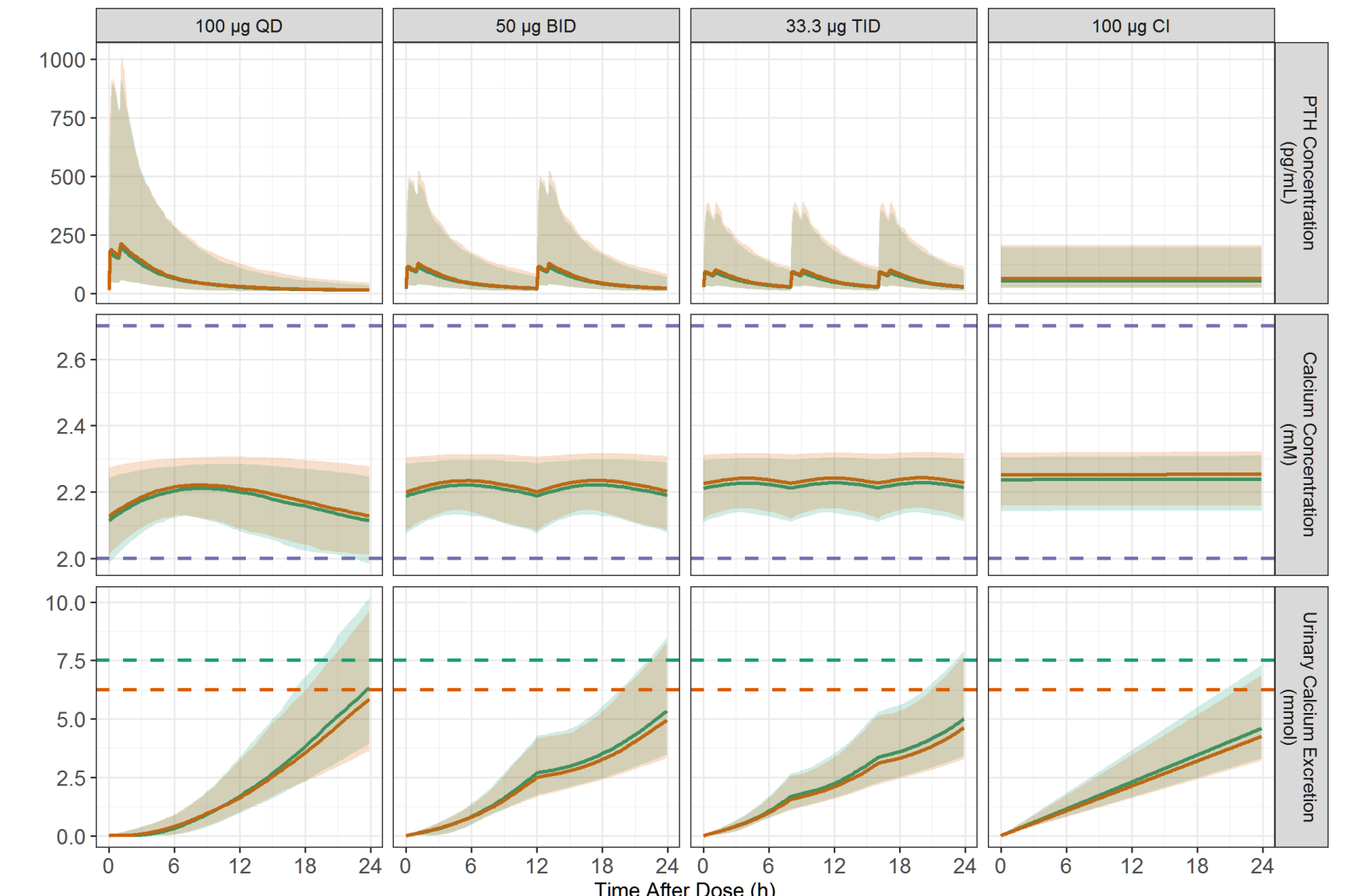
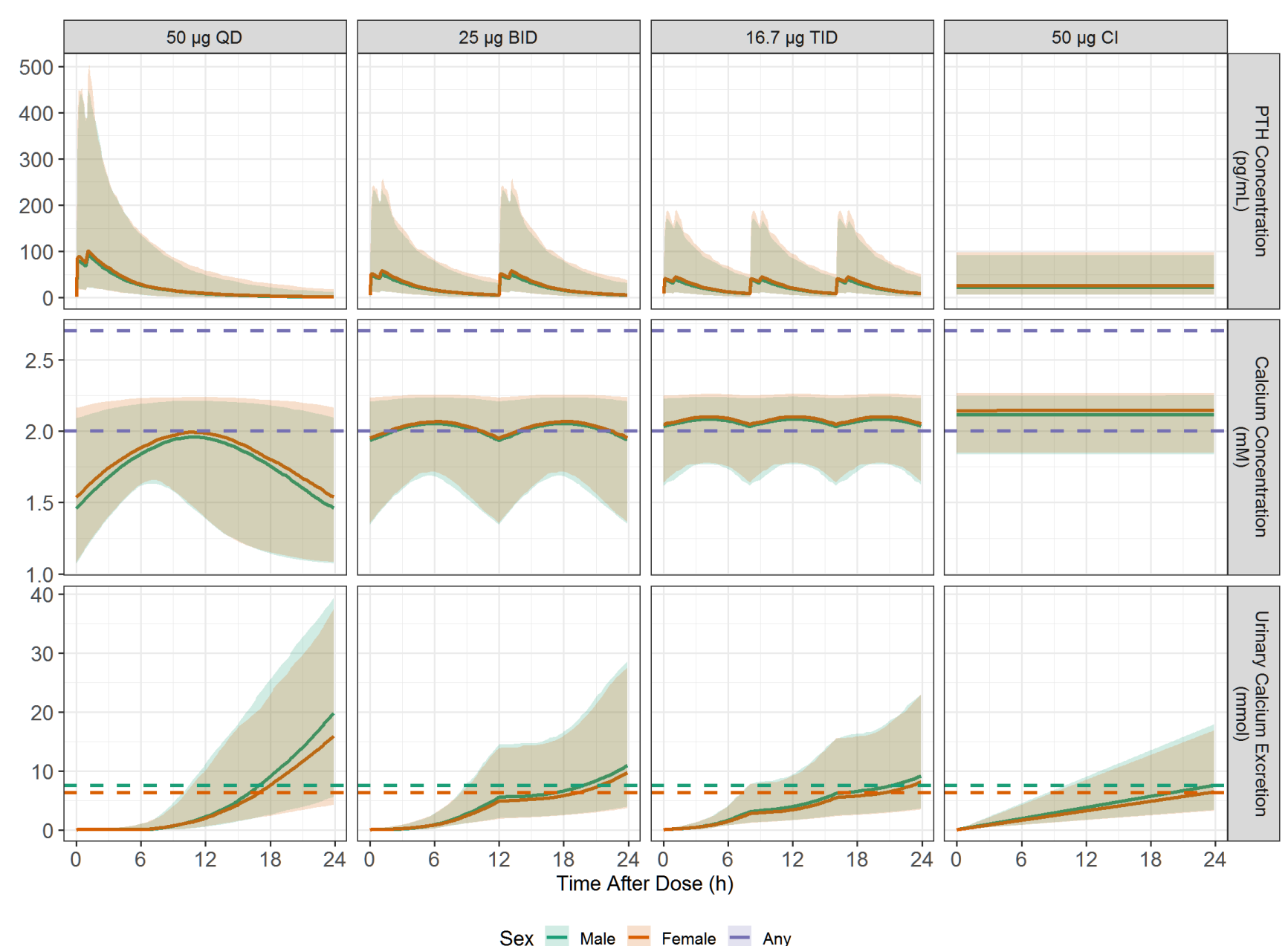


Figure 4. Simulations (50 µg Total Daily Dose)



BID = twice daily; CI = continuous infusion; PTH = parathyroid hormone QD = once daily; TID = thrice daily. Note: Dashed lines represent threshold for normal serum calcium range (blue lines), hypercalciuria (brown and green for female and male, respectively); Solid lines and shaded areas represents the 50<sup>th</sup> percentile (lines) and 90<sup>th</sup> confidence interval (areas) of simulated values.

For QD and BID regimens, serum calcium concentrations are maintained within the target range similar to those from the SOC while urinary calcium excretion is reduced.

The predicted percentage of hypercalciuria (>7.5mmol over 24 hours in males and >6.25mmol over 24 hours in females) for various rhPTH(1-84) QD and BID regimens are presented below.

Regimen	Female	Male
100 µg QD	40.8%	30.6%
50 µg QD	57.0%	45.0%
25 µg QD	74.4%	62.2%
50 µg BID	19.4%	12.4%
25 µg BID	39.6%	28.6%
12.5 µg BID	63.6%	50.8%

## CONCLUSIONS

Both QD and BID dosing regimens of rhPTH(1-84) at daily doses from 25 µg to 100 µg markedly reduced urinary calcium excretion and the possibility of hypercalciuria while maintaining serum calcium level in target range as compared to the SOC.

Although these modeling simulations appear to show that rhPTH(1-84) BID dosing regimens may predict a lower likelihood of hypercalciuria than the QD dosing regimens, clinical data are needed, and a clinical study is planned to confirm these findings.

## REFERENCES

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## DISCLOSURES

Peyret T, Rich B and Marier JF are employees of Certara which was contracted by Shire, a member of the Takeda group of companies, to conduct this research. Song I, Sherry N and Finkelman R, are employees of Shire Human Genetic Therapies, Inc., Lexington, MA, USA, a member of the Takeda group of companies. This research was funded by Shire Human Genetic Therapies, Inc., Lexington, MA, USA, a member of the Takeda group of companies

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