ORIGINAL ARTICLE

Bridging adults and paediatrics with secondary hyperparathyroidism receiving haemodialysis: a pharmacokinetic-pharmacodynamic analysis of cinacalcet

Ping Chen[1] | Winnie Sohn[1] | Adimoolam Narayanan[1] | Per Olsson Gisleskog[2] | Murad Melhem[1]

[1] Amgen Inc., Thousand Oaks, CA, USA

[2] SGS Exprimo, London, UK

Correspondence
Murad Melhem, PhD, Vertex Pharmaceuticals, 50 Northern Avenue, Boston, MA 02210, USA.
Email: murad_melhem@vrtx.com

Aims: The aims of this study were to develop a pharmacokinetic (PK) and PK-pharmacodynamic (PK/PD) model of cinacalcet in adults and paediatrics with secondary hyperparathyroidism (SHPT) on dialysis, to test covariates of interest, and to perform simulations to inform dosing in paediatrics with SHPT.

Methods: Cinacalcet PK, intact parathyroid hormone (iPTH) and corrected calcium (cCa) time courses following multiple daily oral doses (1–300 mg) were modelled using a nonlinear mixed effects modelling approach using data from eight clinical studies. Model-based trial simulations, using adult or paediatric titration schemas, predicted efficacy (iPTH change from baseline and proportion achieving iPTH decrease ≥30%) and safety (cCa change from baseline and proportion achieving cCa ≤8.4 mg/dL) endpoints at 24 weeks.

Results: Cinacalcet PK parameters were described by a two-compartment linear model with delayed first-order absorption-elimination (apparent clearance = 287.74 L h^{-1}). Simulations suggested that paediatric starting doses (1, 2.5, 5, 10 and 15 mg) would provide PK exposures less than or similar to a 30 mg adult dose. The titrated dose simulations suggested that the mean (prediction interval) proportion of paediatric and adult subjects achieving ≥30% reduction in iPTH from baseline at Week 24 was 49% (36%, 62%), and 70.1% (62.5%, 77%), respectively. Additionally, the mean (confidence interval) proportion of paediatric and adult subjects achieving cCa ≤8.4 mg dL^{-1} at Week 24 was 8% (2%, 18%) and 23.6% (17.5%, 30.5%), respectively.

Conclusions: Model-based simulations showed that the paediatric cinacalcet starting dose (0.2 mg kg^{-1}), titrated to effect, would provide the desired PD efficacy (PTH suppression <30%) while minimizing safety concerns (hypocalcaemia).

KEYWORDS
chronic kidney disease, dialysis, modelling and simulation, paediatrics, PK/PD

---

1 | INTRODUCTION

Chronic kidney disease-mineral bone disorder is a complex condition associated with end-stage renal disease (ESRD).[1] Loss of kidney function results in decreased vitamin D synthesis and subsequent hypocalcaemia leading to parathyroid hormone (PTH) overproduction.[2,3] Chronic oversecretion of PTH as chronic kidney disease (CKD) progresses to ESRD acts to mobilize calcium (Ca) from bone, ultimately leading to the syndrome of secondary hyperparathyroidism (SHPT) characterized by deleterious effects on bone, further disturbances in mineral metabolism, particularly Ca and phosphorus (P), and pathological effects in a variety of organ systems including soft tissue and vascular calcification, left ventricular hypertrophy and increased risk for cardiovascular events.[4-8] The deleterious effects of PTH on bone take on added significance in paediatric patients who are at various stages of skeletal development.[9-15]

Therapeutic strategies to control hyperparathyroidism have focused on control of PTH hypersecretion by the parathyroid gland. The parathyroid gland **Ca-sensing receptor** (CaS receptor) is sensitive to changes in extracellular Ca and maintains serum Ca levels through control of PTH secretion and renal Ca reabsorption.[16-18] When serum Ca levels are too low, the parathyroid gland increases secretion of PTH and, conversely, when serum Ca levels increase, PTH secretion is inhibited. The CaS receptor agonists, referred to as calcimimetics, activate the CaS receptor and increase the sensitivity of the CaS receptor to extracellular Ca, thereby signalling the parathyroid to decrease secretion of PTH.[19-21] Calcimimetics have also been shown to inhibit PTH gene expression.[22] **Cinacalcet** is a first-in-class calcimimetic agent that acts as an allosteric modulator of the CaS receptor on the surface of the parathyroid cell, increasing the sensitivity of the CaS receptor to extracellular Ca, ultimately leading to a decrease in PTH secretion.[23] Cinacalcet is extensively metabolized by multiple hepatic cytochrome P450 (CYP) enzymes (primarily 3A4, 2D6 and 1A2) with <1% of the parent drug excreted in the urine.[24] Additionally, cinacalcet is not dialysable during the haemodialysis session. As such, degree of renal impairment and mode of dialysis do not affect the pharmacokinetics (PK) or the pharmacodynamics (PD) of cinacalcet.[25]

Because of the Ca-lowering effects of cinacalcet and associated safety concerns (hypocalcaemia) as well as the potential liabilities of excessive lowering of PTH (below the normal range), the drug should be administered according to a dose titration scheme/algorithm based on PTH and serum Ca levels during treatment. Cinacalcet has been approved by the US Food and Drug Administration and European Medicines Agency for use in adults with dosage guidelines from a titration scheme aimed at lowering PTH and Ca levels with minimal safety risks that may result from extremely low serum Ca levels.[26,27] Despite recent approval for cinacalcet use in paediatrics in Europe, there is a lack of guidance for safe and efficacious dosing in paediatric patients in the US, due to challenges with recruiting patients from a limited population of paediatric dialysis patients and concerns about potential safety issues seen in Phase 3 clinical studies in adults.

What is already known about this subject

- Cinacalcet is a calcimimetic agent for the treatment of secondary hyperparathyroidism in subjects with chronic kidney disease on dialysis. At the time of this analysis, cinacalcet was only approved for use in adults.

What this study adds

- Utility of pharmacokinetic-pharmacodynamic modelling to support bridging cinacalcet effects in adult and paediatric patients.

- These analyses were the basis for selecting dosing algorithms in paediatrics and consequent approval in the EU.

This study reports on a pooled pharmacometric analysis of cinacalcet for treatment of SHPT in adult and paediatric subjects. The primary objective was to develop a PK and PK/PD model of cinacalcet and markers of efficacy (serum PTH concentration) and safety (serum Ca concentration) in order to compare and bridge adult PK and PD parameters with paediatric subjects. Accordingly, the effects of cinacalcet on the time course of PTH and serum Ca in paediatrics were investigated. Covariates of interest were assessed, and model-based simulations were performed to compare PK, PTH and serum Ca between adults and paediatric patients in support of a recommended starting dose and a dose titration scheme aimed to achieve desired efficacy and safety endpoints.

2 | METHODS

2.1 | Study design

Cinacalcet plasma, serum intact PTH (iPTH) and serum corrected Ca (cCa) concentration–time data were obtained from four paediatric clinical studies in CKD patients with SHPT receiving dialysis, and four adult clinical studies, three of which included ESRD patients with SHPT and one in healthy subjects treated with single and multiple doses of cinacalcet (Table 1). Blood samples were collected from adult and paediatric patients with SHPT at predefined time intervals following single or repeated and titrated oral administration (1–300 mg) to assess PK and PD of cinacalcet (Table 1). Recommended cinacalcet starting doses (grouped and based on dry weight to target ≤0.2 mg kg^{-1}) and titration schedules were applied to attain iPTH and cCa within target range while minimizing risk of hypoparathyroidism, hypocalcaemia and the associated adverse events (Supporting Information S2). Study protocols were approved by the institutional review board/independent ethics committee of each study centre. All procedures involving human participants were performed across

TABLE 1 Summary of clinical studies

Study	Phase	Cinacalcet dose	PK, iPTH and cCa sampling scheme	Number of subjects	Population	Associated references
20070208	1	Titrated dose: 2.5–15 mg	PK at predose, postdose on Day 1, Weeks 3, 7, 11, 15, 19 and 23; PD at predose, Weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23	43	CKD/SHPT in child aged 6–18 yr	Warady BA, et al. *Pediatr Nephrol.* 2017;32:1666 (O-55) Warady BA, et al. *Pediatr Nephrol.* 2019;34(3):475–486.
20110100	2	Titrated dose: 1, 2.5, 5, 7.5, 10, 15, 30 and 60 mg	PK at predose, post dose on Weeks 4, 8, 12, 16, 20 and 24; PD at predose, Weeks 3, 7, 11, 15, 19, 22 and 24	17	CKD/SHPT in child aged 28 days–6 yr	Goodman WG, et al. *J Am Soc Nephrol.* 2017;28(FR-PO291)
20030227	1	Single 15 mg	PK/PD at predose, on Day 1 at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48 and 72 h postdose	12	CKD/SHPT in child aged 6–17 yr	Chen P, et al. *J Pharmacokinet Pharmacodyn.* 2018; 10:S81(T-079)
20090005	1	Single 0.25 mg kg^{-1}	PK at 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (Day 2), 48 (Day 3) and 72 h (Day 4) postdose; PD at predose, Days 1 and 4	12	CKD/SHPT in child aged 28 days–6 yr	Warady BA, et al. *Pediatr Nephrol.* 2017;32:1715 (P-119) Sohn WY, et al. *Pediatr Nephrol.* 2019;34:145–154 Chen P, et al. *J Pharmacokinet Pharmacodyn.* 2018;10:S81(T-079)
20000172	3	Dose titration Q3W: 30, 60, 90, 120 and 180 mg	PK at predose, 2, 4 and if possible 6 h postdose on Week 24. Trough samples on Weeks 2, 5, 11 and 16. Weekly trough samples throughout dose-titration and biweekly throughout efficacy stage	403	ESRD with SHPT in adults	Martin KJ, et al., *Kidney Int.* 2005;68:1236–1243
20000187	1	Dose titration QW dose adjustment: 25, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275 and 300 mg	PK trough samples on Days 4, 6 and 7 of each dose level. PK/PD at predose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h postdose on Day 7 of each dose level. Additional PK samples at 48, 72, 96 and 120 h after final dose	22		n/a
980126	2a	Single dose in part 1 with a 4 week wash out then 8 QD doses in part 2: 5, 10, 25, 50, 75 and 100 mg	Intensive PK/PD over 72 h after single dose in (P1) and over 24 h after QD (P2) dosing on Days 1 and 8. At 24 h postdose on Days 2–7, and at 48 and 72 h postdose on Days 8 and 15 (P2)	60		n/a
970241	1	Single and multiple dose: 1, 5, 25, 50 or 100 mg	Intensive PK at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48 and 72 h postdose. PD at predose, 0.5, 1, 2, 4, 8, 12, 18, 24, 48 and 72 h postdose	79	Healthy adult subjects	n/a

cCa, corrected serum calcium levels; CKD, chronic kidney disease; ESRD, end-stage renal disease; iPTH, intact parathyroid hormone levels; n/a, none associated; P1, part 1; P2, part 2; PD, pharmacodynamic; PK, pharmacokinetic; Q3W, every 3 weeks; QD, once a day; QW, weekly; SHPT, secondary hyperparathyroidism.

multiple centres in accordance with the local ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study, and/or their parent or legally acceptable representative.

2.2 | Analytical methods/assay PK and PD parameters

Cinacalcet plasma concentrations were analysed by a validated liquid chromatography/mass spectrometry method (lower limit of quantitation = 0.1 ng ml^{-1}); iPTH serum concentrations were determined using an immunometric assay (ADVIA Centaur® PTH Assay, Siemens Healthcare, Erlangen, Germany) with a lower limit of quantitation = 10.5 pg ml^{-1}; and cCa concentrations using standard methods.[28] Further details (internal standard, precision and interday variability) on the non-commercial assays used are provided in Supporting Information S1. A total of 2994 (34.7%) PK cinacalcet concentrations were below the lower limits of quantification and were subsequently excluded from further analyses.

2.3 | Model development and covariate analysis

The pooled dataset was divided into two datasets: an index dataset which constituted 70% of the total data and a test dataset which constituted 30% of the total data. Division of the pooled dataset was performed randomly but ensured that different age groups of the paediatric subjects were represented in similar proportions in index and test datasets. The final index and test datasets reflected comparable demographics to the combined dataset. Data from the index dataset were used to develop a PK and PK/PD model and to evaluate the effects of relevant covariates on PK and PK/PD model parameters. Data from the test dataset were used to externally evaluate the model. Data from the pooled dataset were subsequently used to update the model and quantify the model parameters and the final analysis of covariate effects of covariates on PK and PK/PD parameters.

Variations of simple direct or indirect response PK/PD models were explored graphically as potential model structures that may describe the time courses of iPTH and cCa, based on physiological/ pathophysiological knowledge. Additional mechanism-based components that quantitatively describe the physiological interaction between the iPTH, cCa and cinacalcet (allosteric activation) were also evaluated as part of the structural model. These components were physiologically relevant and eventually deemed appropriate to characterize the time courses of iPTH and cCa (Figure 1).

Covariate analysis was conducted using stepwise forward selection (α = 0.005), followed by a backward elimination approach (α = 0.001). Baseline covariates included: subject demographics (age as continuous or categorical variable [adults vs paediatric categories], body weight, body surface area, gender and race), liver function biomarkers (aspartate aminotransferase, alanine aminotransferase, serum albumin, total bilirubin), alkaline phosphatase, iPTH, cCa, P, serum creatinine, use of concomitant medications (vitamin D, phosphate binders and Ca supplements).

The established PK and PK/PD models were evaluated using standard goodness-of-fit diagnostic plots, internal prediction-corrected visual predictive checks (pcVPC) and external pcVPC against the test dataset. Residual variability parameters were used for PK, iPTH and cCa using additive error models after natural logarithmic transformation of the measured concentrations and model predictions. Cinacalcet initial half-life for paediatrics across all age groups was calculated based on median estimates of clearances and volumes of distribution. The effective half-life in paediatrics across all age groups and adults was calculated based on the accumulation ratio on Day 10.

2.4 | Model-based trial simulations

Model-based simulations were used to explore and compare the PK properties, exposure–response relationship, as well as predict the efficacy and safety profiles following treatment with cinacalcet
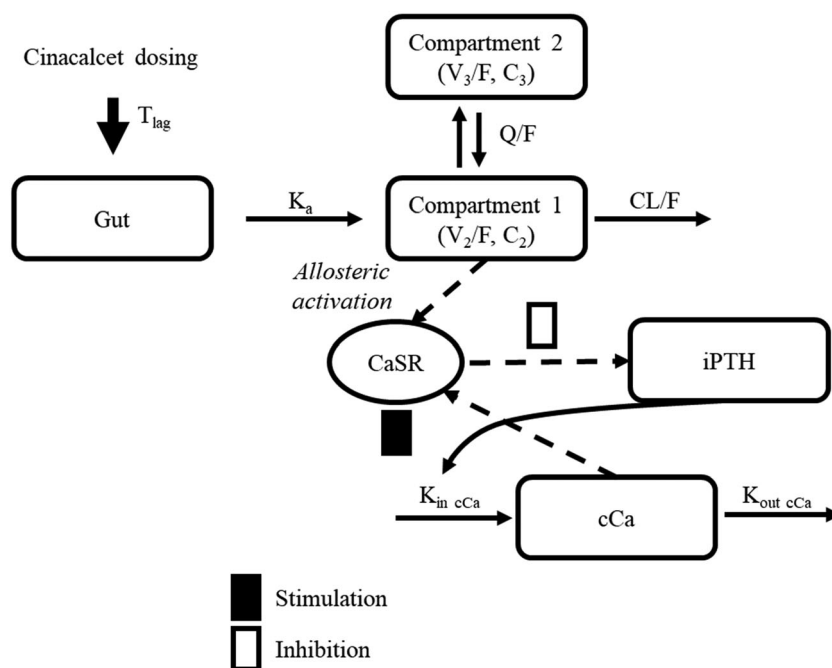
FIGURE 1 PK/PD model schematic. CaS receptor, calcium-sensing receptor; cCa, corrected calcium; CL/F, apparent systemic clearance; iPTH, intact parathyroid hormone; $K_{in\ cCa}$, the first order input rate for Ca; $K_{out\ cCa}$, the first order elimination rate for Ca; Q/F, apparent distribution clearance; T_{lag}, lag time

implementing the dose titration algorithms in both adult and paediatric subjects. The median PK, iPTH and cCa time-course profiles were summarized and plotted based on age/weight cutoffs as evaluated in clinical development and/or recommended in the Summary of Product Characteristics (SmPC, Supporting Information S2). Additionally, for each dose group, the median and 90% prediction interval (PI) of the time courses of cinacalcet concentration, and the resulting iPTH and cCa, were also graphically represented and visually compared.

2.4.1 | Simulations to compare exposure from a 30 mg adult dose across increasing doses in paediatrics

Time courses of cinacalcet PK, iPTH and cCa in paediatric subjects were simulated with doses ranging from 1 to 180 mg across paediatric age groups according to doses recommended in the SmPC (Supporting Information S2). Adult simulations at the starting dose of 30 mg were also simulated. Realistic age-weight-sex distributions for paediatric population age 28 days–18 years were obtained by randomly and jointly sampling patients' age, weight and sex combinations from the National Health and Nutrition Examination Survey paediatric demographic database.[29,30] Weights for adult patients were sampled from demographics in cinacalcet clinical trials. The median and 90% PI of PK, iPTH and cCa time-course profiles were summarized and plotted based on age/weight cutoffs recommended in the SmPC.

2.4.2 | Simulations to compare current treatment algorithms in adults to paediatric label-proposed dosing algorithms

To evaluate the titration dose algorithm in paediatric subjects and to compare to cinacalcet effects in adults, the final PK/PD model was used to simulate time courses of cinacalcet exposures, iPTH and cCa. These simulations were performed employing the approved treatment algorithm in adults and the label-proposed treatment algorithm in paediatric subjects.

In adults, model-based simulations were performed in accordance with Study 20000172 design[31] with no dropouts (NCT00037635) (Supporting Information S3). In paediatrics, the dose titration algorithm and Ca monitoring schedule proposed on the label, combined with study design characteristics from Study 20070208[32] (NCT01277510) (Supporting Information S4) were used as the basis for the paediatric titration simulations.

Simulations were run to evaluate the mean and 95% PIs for the efficacy and safety metrics of weekly cCa monitoring. The details of the dosing algorithm and inclusion criteria for simulation are shown in Supporting Information S3–S5. Over 24 weeks of treatment, the following endpoints were summarized and compared: (a) PTH change from baseline *vs* time; (b) Fraction of subjects with iPTH decrease ≥30% *vs* time; (c) cCa change from baseline *vs* time; and (d) Fraction of subjects with cCa ≤8.4 mg dL^{-1}. A 30% reduction from baseline iPTH represents the maximal suppression of PTH induced by hypercalcaemia or following parathyroidectomy and indicates the

normalization of parathyroid function.[33] Furthermore, a 30% reduction corresponds to the iPTH primary clinical endpoint target on which cinacalcet approval in adults was based.

2.5 | Statistical considerations

A series of the models (described above) were evaluated to identify the most preferable structural and statistical models. A preferable model was defined as one that converged successfully, had a successful estimation of the standard errors, produced reasonable parameter estimates, improved the goodness-of-fit graphics, and had low inter- and intra-individual variability. In addition, for each model, the improvement in the fit obtained was assessed by examination of several diagnostics.

2.6 | Software

Population PK and PK/PD modelling were performed using a nonlinear mixed effects modelling approach with NONMEM 7.2 software. Paediatric trial simulations with adaptive drug titration were performed with Simulo version 5.3.2. (SGS-Exprimo), which is a JAVA-based software creating and running R scripts (version 2.14.2). Data manipulation and graphical presentations were performed in R version 3.1.0.

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to Pharmacology,[34] and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.[35]

3 | RESULTS

Cinacalcet plasma concentration–time profiles in healthy subjects or patients with SHPT receiving haemodialysis showed that plasma cinacalcet concentrations declined over time in a bi-exponential manner in both adult and paediatric subjects. Cinacalcet PK were adequately described by a two-compartment linear model with delayed first-order absorption and first-order elimination from the central compartment following single and/or multiple oral dosing in healthy subjects or patients with SHPT receiving haemodialysis (Figure 1). Steps to derive a semi-mechanistic PK/PD model to characterize the interplay between cinacalcet, iPTH and cCa, including the role of PTH in Ca regulation, the feedback of Ca onto PTH production via the CaS receptor, and the activity of cinacalcet plasma levels in increasing the sensitivity of the CaS receptor to Ca via cooperative binding are described in Table 2 and depicted in Figure 1.

The PK and PD parameter estimates are summarized in Tables 3 and 4, respectively. All PK parameters were estimated with good precision (relative standard error [RSE] % <20%). No evidence of dose- or

TABLE 2   Definition of terms and derivations of the semi-mechanistic model

Mechanistic component	Key assumptions	Considerations
Equation 1. Fractional occupancy of CaS receptor by ionized Ca in the absence of drug $$\rho = \frac{Ca}{K_D + Ca}$$	• cCa production is stimulated by increases in iPTH from baseline • iPTH production is directly inhibited by changes in CaS receptor occupancy by the innate ligand, ionized Ca, relative to the baseline (no cinacalcet treatment) occupancy • K_D, the equilibrium dissociation constant of ionized Ca, was assumed to be 1.2 mM.[36] Ionized Ca was calculated empirically as 0.45 of cCa.[28] • The fractional change in CaS receptor occupancy relative to baseline is the driving force for iPTH production in the absence of rich iPTH data at early time points following dosing	iPTH turnover is very rapid, and due to the relative sparseness of PTH data in the early period following dosing, the expected temporal dissociation from cinacalcet pharmacokinetics was not apparent in the available sparse data
Equation 2. Pseudo steady-state model $$iPTH = iPTH_0 \cdot \left(\frac{\rho}{\rho_0}\right)^\lambda$$	• iPTH levels are directly related to CaS receptor occupancy • $iPTH_0$ is the baseline iPTH level • p0 is the ionized Ca/CaS receptor occupancy at baseline • λ is a constant determining the strength of the effect of changes in ρ on iPTH production	As an increase in receptor occupancy is expected to lead to a decrease in iPTH production rate, λ is expected to be negative.
Equation 3. cCa turnover $$\frac{dcCa}{dt} = K_{in,Ca}\left(\frac{iPTH}{iPTH_0}\right)^\gamma - K_{out,Ca} \cdot cCa$$	• $K_{in,Ca}$ is the zero-order production rate of cCa • Gamma (γ) is the power relating changes in iPTH from baseline to Ca production • $iPTH_0$ is baseline iPTH and $K_{out,Ca}$ is the first order elimination rate for Ca	By amalgamating the Ehlert model for receptor allosterism[37] and the operational model of agonism,[38] a model can be obtained which characterizes the effects of a modulator on endogenous ligand effect[39,40]
Equation 4. Fractional occupancy of CaS receptor by ionized Ca in the presence of cinacalcet $$\rho = \frac{\dfrac{Ca}{K_D}\left(1 + \dfrac{\alpha \cdot C_p}{K_i}\right)}{\dfrac{Ca}{K_D}\left(1 + \dfrac{\alpha \cdot C_p}{K_i}\right)\dfrac{C_p}{K_i} + 1}$$	• Cinacalcet increases the affinity of the CaS receptor for Ca, thus leading to an increased CaS receptor occupancy by Ca and stimulation of PTH production for the same Ca concentration • K_i is the equilibrium dissociation constant for cinacalcet at the CaS receptor • α is the cooperativity constant, and C_p is the cinacalcet plasma concentration • If α is <1, the interaction is negatively cooperative • If α is >1, the interaction is positively cooperative (i.e., the affinity of the CaS receptor for Ca is increased)	Due to the limited number of samples collected for iPTH, particularly early in the profile, available data did not support full characterization of both K_i and α. C_p/K_i is negligible
Equation 5. Fractional occupancy of CaS receptor by ionized Ca in the presence of cinacalcet (simplified) $$\rho = \frac{\dfrac{Ca}{K_D}(1 + Ratio \cdot C_p)}{\dfrac{Ca}{K_D}(1 + Ratio \cdot C_p) + 1}$$	• Simplification of Equation 4 using the following allosteric ratio: $$Ratio = \frac{\alpha}{K_i}$$	

(Continues)

BRITISH PHARMACOLOGICAL SOCIETY

TABLE 2 (Continued)

Mechanistic component	Key assumptions	Considerations
Equation 6. Baseline cCa values $K_{in,Ca} = Ca_0 \cdot K_{out,Ca}$	• cCa_0 is the estimated baseline cCa value • $K_{in,Ca}$ is the zero-order production rate of cCa	Visual inspection of individual cinacalcet PK, iPTH and cCa concentrations vs time profile suggested that model parameters varied between subjects. As a consequence, between-subjects variability (inter-individual variability, IIV) in a model parameter, P, was included in the model and was assumed to be log-normally distributed
Equation 7. Accounting for inter-individual variability in model parameters $P_j = P \times e^{\eta_j}$	• P_j is the model parameter for the jth individual • $P*$ is the population typical value for the model parameter; η_j is a random II effect and it is assumed to be a random Gaussian variable with zero mean and variance ω^2	Residual variability parameters were used for PK, iPTH and cCa using additive error models after natural logarithmic transformation of the measured concentrations and model predictions

TABLE 3 Parameter estimates and relative and associated precisions for the final population PK model

Parameter	Estimate	RSE (%)
K_a (L h^{-1})	0.80	10
CL/F (L h^{-1})	287.74	4.7
V_2/F (L)	4104.15	6.78
V_3/F (L)	19824.20	10.2
Q/F (L h^{-1})	296.3	7.3
T_{lag} (h)	0.36	0.02
ω_{Ka} (% CV)	102	20.2
$\omega_{CL/F}$ (% CV)	76	9.19
Correlation between CL/F and V_2/F	0.85	11.5
$\omega_{V2/F}$ (% CV)	69	17
$\omega_{V3/F}$ (% CV)	86	16.1
$\omega_{Q/F}$ (% CV)	68	18.6
ω_{Tlag} (% CV)	34	51.4
$\sigma_{other\ studies\ prop}$ (% CV)	50	1.48
$\sigma_{Ph3\ studies\ prop}$ (% CV)	72	2.8

CL/F, apparent systemic clearance; CV, coefficient of variation; K_a, absorption rate constant; Q/F, apparent distribution clearance; RSE, relative standard error; T_{lag}, lag time; V_2/F and V_3/F, apparent volume of distribution for the central and peripheral compartments, respectively; $\sigma_{Ph3\ studies\ prop}$ and $\sigma_{other\ studies\ prop}$, proportional residual error expressed as additive error on log scaled DV for Phase 3 studies and other studies, respectively; ω_{Ka}, $\omega_{CL/F}$, $\omega_{V2/F}$, $\omega_{V3/F}$, $\omega_{Q/F}$, and ω_{Tlag}, inter-individual variability (expressed in % CV) on K_a, CL/F, V_2/F, V_3/F, Q/F and T_{lag}, respectively.

time-dependent PK was observed with cinacalcet. The estimates of IIV on the apparent systemic clearance (CL/F) and apparent central volume of distribution were relatively high (76% coefficient of variation [CV] and 69% CV, respectively; Table 3). Covariate analysis found no statistically significant or clinically relevant predictors of PK parameters. However, due to a lower percentage of paediatric subjects in the dataset relative to adults, the impact of body weight may not be apparent. Allometric scaling with the exponent fixed to 0.75 for CL, and 1 for V_1, were included in the final PK model. All PD parameters were estimated with good precision (RSE% <30%).

The model suggested a slow turnover of Ca with a half-life of 23.1 hours. The power on the change of receptor occupancy (γ) was estimated to be −3.3. This value reflected the steep effect of change of CaS receptor occupancy on PTH dynamics. The ratio was a descriptor of drug potency and was estimated to be 0.072 mM^{-1}, the positive value indicating that cinacalcet increases Ca potency at the CaS receptor. Inter-individual variability in allosteric ratio, power on change in iPTH, and power on change in receptor occupancy were relatively high (78–133% CV). Baseline age, weight, race, sex and P were assessed as covariates, none of which were identified as statistically significant predictors of PD variability.

The internal pcPVC for the final PK/PD model for iPTH and cCa, separated by age group, is shown in Figures 2A and 2B, respectively. The bulk of the data fell within the prediction-corrected PIs. Trends in the prediction-corrected observed (blue circle) data were

TABLE 4 Parameter estimates and associated precisions for final population PK/PD model

Parameter	Estimate	RSE (%)
PTH$_{0\ Patient}$ (pM)	54.29	2.91
Ca$_{0\ Patient}$ (mM)	2.45	0.30
Ratio$_{Patient}$ (L mM^{-1})	0.072	8.09
K$_{out,Ca\ Patient}$ (L h^{-1})	0.03	16.89
Power on PTH$_{Patient}$	0.07	10.11
Power on RO$_{Patient}$	−3.30	−6.20
PTH$_{0\ HV}$ (pM)	2.38	19.39
K$_{out,Ca\ HV}$ (L h^{-1})	0.01	20.01
Power on RO$_{HV}$	−10.03	−13.24
Ratio$_{HV}$ (L mM^{-1})	0.02	18.85
Power on PTH$_{HV}$	1.80	43.22
Ca$_{0\ HV}$ (mM)	2.30	1.67
ω$_{PTH0}$ (% CV)	64.00	3.92
ω$_{Ca0}$ (% CV)	6.60	6.20
ω$_{Ratio}$ (% CV)	80.51	12.39
ω$_{Power on PTH}$ (% CV)	112.51	13.17
ω$_{Power on RO}$ (% CV)	75.07	10.51
σ$_{iPTH\ Patient}$ (% CV)	43	0.26
σ$_{cCa\ Patient}$ (% CV)	7	0.26
σ$_{iPTH\ HV}$ (% CV)	23	1.39
σ$_{cCa\_HV}$ (% CV)	3.73	1.03

Ca$_{0\ Patient}$ and Ca$_{0\ HV}$, baseline Ca level for patient and healthy subjects, respectively; CV, coefficient of variation; K$_{out,Ca\ Patient}$ and K$_{out,Ca\ HV}$, the first order elimination rate for Ca for patient and healthy subjects, respectively; PTH$_{0\ Patient}$ and PTH$_{0\ HV}$, baseline iPTH level for patient and healthy subjects, respectively; Power on PTH$_{Patient}$ and Power on PTH$_{HV}$, the power relating changes in iPTH from baseline to Ca production for patient and healthy subjects, respectively; Power on RO$_{Patient}$ and Power on RO$_{HV}$, a constant determining the strength of the effect of changes in receptor occupancy (RO) on iPTH production for patient and healthy subjects, respectively; Ratio$_{Patient}$ and Ratio$_{HV}$, for patient and healthy subjects, respectively; RO, receptor occupancy; RSE, relative standard error; ω$_{PTH0}$, ω$_{Ca0}$, ω$_{Ratio}$, ω$_{Power on PTH}$ and ω$_{Power on RO}$, inter-individual variability (expressed as % CV) on PTH$_0$, Ca$_0$, ratio, power on PTH, and power on RO, respectively; σ$_{iPTH\ Patient}$ and σ$_{iPTH\ HV}$, proportional residual error expressed as additive error on log scaled iPTH for patients and healthy subjects, respectively; σ$_{cCa\ Patient}$ and σ$_{cCa\ HV}$, proportional residual error expressed as additive on log scaled Ca for patients and healthy subjects, respectively.

adequately captured by the corresponding simulation-based prediction-corrected median and the 95% PI. The external pcVPC is shown in Supporting Information S10.

Simulation data suggested that the starting dose for paediatrics <2 years (1 or 2.5 mg), 2–6 years (1, 2.5 or 5 mg), and 6–18 years (2.5, 5, 10 or 15 mg), respectively, would provide lower or similar PK exposure compared with a 30 mg dose in adults (Supporting Information S6–S7).

The median half-life (distribution phase; describing the majority of cinacalcet exposure) in paediatric and adult subjects was 2.29 and 4.27 hours, respectively. This estimate is in line with the expected PK behaviour of cinacalcet,[24,41] and is consistent with the previously reported half-life estimate of 6 hours.[24] Consistent with the previous estimate of 30–40 hours for elimination half-life cited,[24] simulation results suggested that >95% steady-state levels of cinacalcet in paediatrics were achieved within 7 days with a median accumulation ratio of 1.93 across all paediatric ages, as compared to 1.69 in adults.

Furthermore, trial simulation data suggested that multiple dosing of the starting dose in paediatrics specified by age (<2 years [1 or 2.5 mg]; 2–6 years [1, 2.5 or 5 mg]; 6–18 years [2.5, 5, 10 or 15 mg]) or weight (5–12.5 kg [1 mg]; 12.5–25 kg [2.5 mg]; 25–50 kg [5 mg]; 50–75 kg [10 mg]; >75 kg [15 mg]) would provide iPTH and Ca reductions comparable to or less than that predicted for the 30 mg multiple dosing in adults at Week 4 (Supporting Information S8–S9).

Compared to paediatric subjects (titrated dosing schema from paediatric Study 20070208), the reduction of PTH and cCa over time appear more apparent in adults (dosing implemented in Study 20000172) (Figure 3). The proportion of paediatric and adult subjects on each dose group is shown in Figure 4A and 4B, respectively. The predicted mean dose level at Week 24 was 34.8 mg and 134 mg, in paediatrics and adults respectively. The predicted dose *vs* time over the course of the study revealed increases in the proportion of patients taking doses between 30 and 180 mg over time, with the first appearance of 180 mg around Week 20 and 12, for paediatric subjects and adults, respectively (Figure 4).

The results of iPTH and cCa reduction following different titrated dosing schema (1 or 2.5 mg [<2 years], 1, 2.5 or 5 mg [2–6 years], and 2.5, 5, 10 or 15 mg [6–18 years]), within the efficacy assessment period are also summarized in Table 5. In paediatric subjects, the mean (PI) proportion of paediatric subjects achieving ≥30% reduction in PTH from baseline and cCa ≤8.4 mg dL^{-1} at Week 24 was 49% (36%, 62%) and 8% (2%, 18%), respectively. The mean (PI) proportion of adult subjects achieving ≥30% reduction in PTH from baseline and cCa ≤8.4 mg dL^{-1} at Week 24 was 70.1% (62.5%, 77%) and 23.6% (17.5%, 30.5%), respectively, following adult Study 20000172 dosing schema.

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices/.

4 | DISCUSSION

A semi-mechanistic population PK/PD model was developed to describe cinacalcet PK, and the quantitative relationship between cinacalcet PK, iPTH and cCa that allowed for exploration of covariates as potential predictors of cinacalcet PK and PD responses based on clinical data from paediatric and adult subjects. The approach allows analysis of PD data from titration schemes that are difficult to interpret with conventional approaches[42] and can be especially useful in the evaluation of dose titration regimens and clinical study designs for paediatric subjects with limited available data. Model evaluation results confirmed the stability and predictive ability of the model developed, as well as quantified precision of the parameter estimates. The model is in agreement with known (or previously reported) PK and PD properties of cinacalcet.[24]
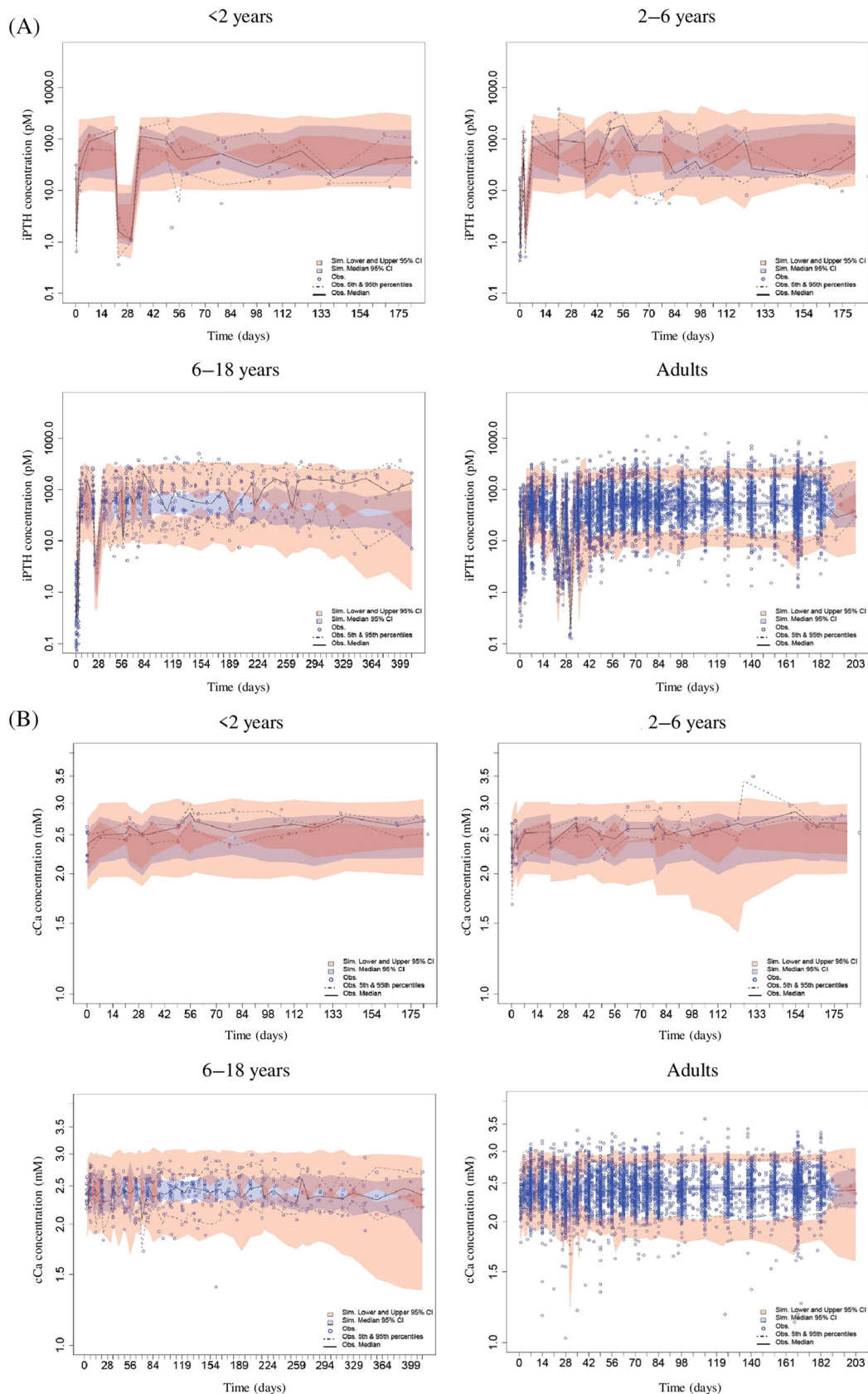
FIGURE 2 Prediction-corrected visual predictive check for the final PK/PD model (combined dataset with additional 5 subjects in Study 20110100) for iPTH A, and corrected calcium B, separated by age group. Note that the bulk of the data fell within prediction-corrected prediction intervals. cCa, corrected calcium; CI, confidence interval; iPTH, intact parathyroid hormone; Obs, observed; PK/PD, pharmacokinetics/pharmacodynamics; Sim, simulated

I.

(A)

(B)

(C)

(D)

II.

(A)

(B)

(C)

(D)
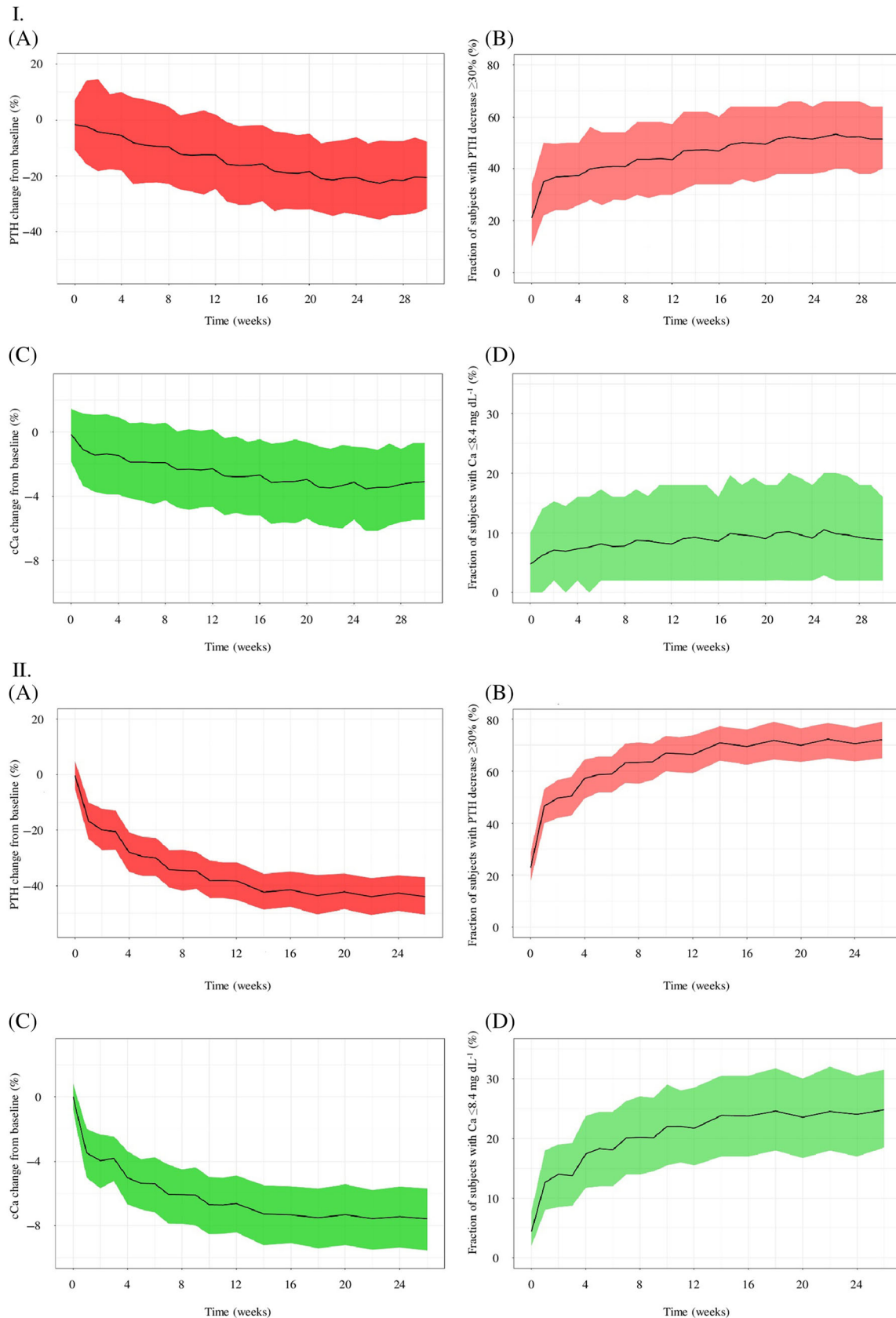
FIGURE 3 Simulated serum iPTH and cCa following Study 20070208 titrated dosing schema with weekly cCa monitoring in paediatric subjects (I), or following study titrated dosing schema in adults (II): A, PTH change from baseline *vs* time; B, fraction of subjects with iPTH decrease ≥30% *vs* time; C, corrected Ca change from baseline *vs* time; D, fraction of subjects with Ca ≤8.4 mg dL^{-1}. Black line and shaded area indicates the mean and 90% prediction interval, respectively; cCa, corrected calcium; iPTH, intact parathyroid hormone

(A)

(B)
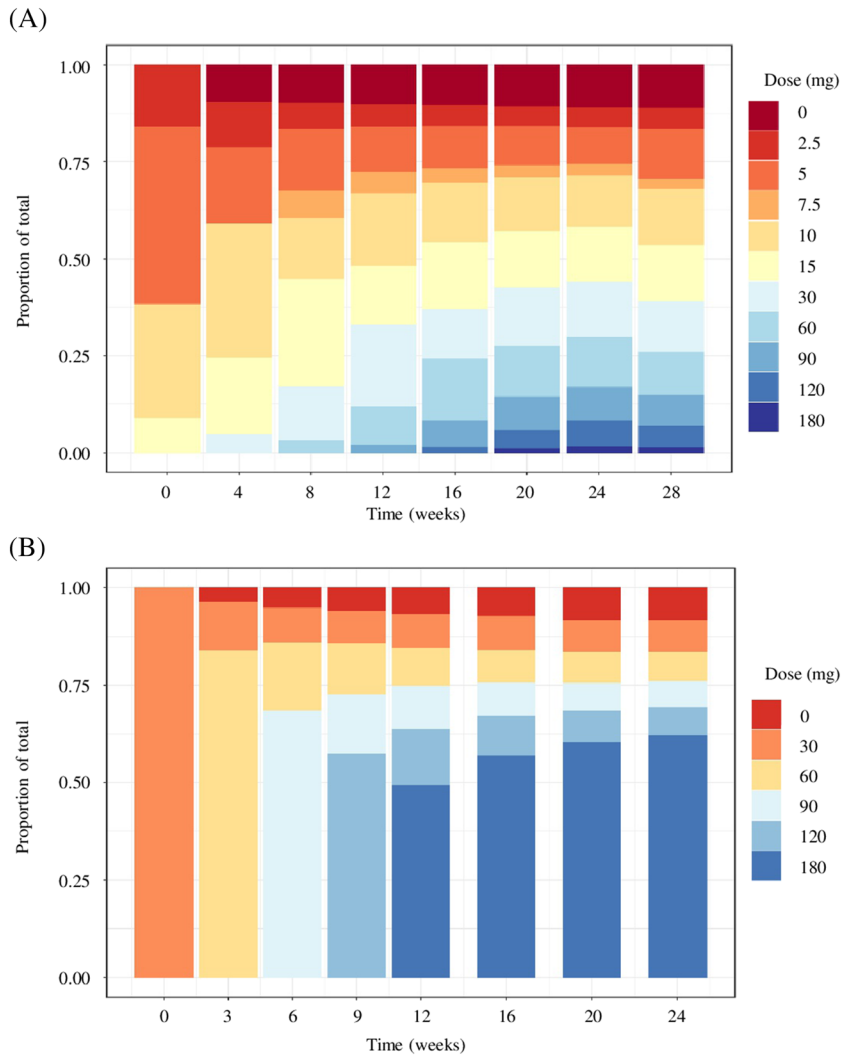
FIGURE 4 The predicted proportion of subjects to be on each dose level, over the course of the study. Simulations were performed following the design and six step-wise titrated dosing schema from paediatric Study 20070208 A, or following dosing implemented in study 20000172 in adult subjects B. Subject to maintenance of serum iPTH and serum calcium values, subjects were eligible for a dose increase once every 4 weeks. For paediatric subjects, next dose level was based on subject post-dialysis weight (see Supporting Information S4.1). cCa, corrected calcium; iPTH, intact parathyroid hormone

TABLE 5 Summary of PTH and cCa reduction at Week 24 in paediatric and adult subjects

Metric	Paediatric[a]	Adults[b]
Mean (PI) proportion of subjects ≥30% from baseline (%) – Week 24	49 (36, 62)	70.1 (62.5, 77)
Mean (PI) PTH change from baseline (%) – Week 24	−20.76 (−33.19, −7.11)	−42.1 (−48.4, −35.6)
Mean (CI) change in cCa from baseline (%) – Week 24	−3.33 (−5.99, −0.82)	−7.4 (−9.2, −5.4)
Mean (CI) proportion of subjects with cCa <8.4 (%) – Week 24	8 (2, 18)	23.6 (17.5, 30.5)

[a]Simulation using Study 20070208 titrated dose schema except replacing bi-weekly cCa monitoring with weekly cCa monitoring.

[b]Simulation using Study 20000172 titrated dose schema.

cCa, corrected calcium; CI, confidence interval; PI, prediction interval; PTH, parathyroid hormone.

The final PK model that included linear elimination and body weight effects with fixed exponents to standard allometric exponents on CL and volume terms resulted in the best fit among several models tested. The results reported herein are generally consistent with previous analyses, in which systemic cinacalcet exposure followed linear and non–time-dependent PKs, with the estimated population CL/F consistent with previous population analyses.[24,43] Following oral administration, absorption from gastrointestinal tract was relatively fast in both adults and paediatrics. There was notable

IIV in PK parameters (CV% 34–102%), with the greatest variability observed for absorption rate. The estimated central volume of distribution was approximately 1.5-fold higher than previously reported. This was thought to be attributed to variability in blood sampling and sparse sampling schemas commonly applied during the absorption/distribution phases in paediatric trials.

Patients receiving dialysis commonly present with multiple comorbid conditions and multiple concurrent therapies, especially those utilized to control serum biochemical and mineral levels, such

as vitamin D sterols, Ca supplements and phosphate binders. Although none of the patient and disease covariates evaluated, including demographic factors, organ function biomarkers, disease characteristics and concomitant medications, were statistically significant predictors of PK parameters across the entire patient population, the paediatric population represented <15% of the total samples. To account for an effect of body weight on the PK parameters that may have been masked by the small proportion of paediatric patients, we included body weight in the PK model with fixed exponents to standard allometric scaling factors for clearance and the apparent volume of distribution for the central compartment, in agreement with allometric theory.[44]

Ca homeostasis is mediated by a complex network of molecular and cellular interactions, with roles for PTH, P, vitamin D, bone metabolism and renal function, all of which must be considered in a truly predictive model. While multiple mathematical and systems models have integrated many of these factors for healthy subjects, and for those with bone and/or CKD,[38,45,46] the mechanistically and physiologically relevant population approach used in the current analysis provides complementary information including residual and IIV in addition to drug effect parameters. Moreover, although similar models describing the time course of iPTH and/or cCa have been reported,[47,48] they did not include the mechanism-based components of allosteric activation and the physiologic feedback mechanisms described in the current model.

Under physiologic conditions, serum Ca concentrations are maintained within a narrow range, despite widely varying environmental factors, such as Ca intake and vitamin D levels, highlighted by the <10% interpatient variability observed in baseline cCa levels. Primary mechanisms of Ca homeostasis (intestinal Ca absorption, renal reabsorption and Ca release from bone),[46] are regulated predominantly by PTH or vitamin D.[42] Physiologic PTH levels can exhibit considerable variability and, given the lack of vitamin D dosing information in the covariate analysis and the importance of PTH in renal and bone Ca absorption, the effect of PTH on Ca levels was an integral component of the current model. This is consistent with both our current understanding of Ca physiology, and with the better fit to the data than an inhibitory effect of PTH on Ca elimination. Moreover, both the effect of PTH on Ca levels, and the variability in PTH levels, mediated through the activity of the CaS receptor,[49] is modelled in the relative sizes of the scaling factors for the two effects, the high power on the change of receptor occupancy for the effect of Ca on PTH production and the small power on the change of PTH for the effect of PTH on Ca production.

Considering the interrelationship between Ca and known mechanisms of PTH secretion, we modelled the effect of Ca on PTH through a receptor-binding model, whereby free Ca interacts with CaS receptor to inhibit PTH secretion.[42] This is in agreement with the known mechanism of cinacalcet regulation of PTH secretion.[23] Ca modelled using an indirect response model yielded an estimated first-order elimination rate for Ca ($K_{out,Ca}$) of 0.03 h^{-1}, with a corresponding Ca serum half-life of approximately 23.0 hours, consistent with what has been reported previously.[50] This means that while there was a rapid decrease in the

iPTH time course following cinacalcet administration, there was a time delay between peak drug concentrations and Ca response.

As complex changes in physiology due to growth and maturation may lead to age-related changes in PK for paediatric patients, evaluating the impact of developmentally dependent (ontogeny) expression of drug metabolizing enzymes may be important to understand the PK in paediatric subjects. Given the multiple routes for CYP450-mediated cinacalcet metabolism and elimination, any fluctuations in enzyme expression in paediatric patients under 2 years of age are not expected to notably affect cinacalcet exposures compared to older paediatric patients. In addition, any changes in enzymatic activity have typically resulted in lower drug absorption and exposure in infants than in older children and adults, and should be considered when constructing PK/PD models for paediatrics.[44] However, in children 2 years of age and older, PK parameters can be reasonably predicted from adult data using size differences in PK.[51] No data from infants under 2 years of age were included in the analysis dataset used for modelling in this study. Accordingly, the need to consider enzymatic activity maturation in our analyses was deemed unnecessary.

Within the range of patient-related, and disease-specific covariates evaluated, there were no statistically significant predictors of PD parameters. Of note, plots of post hoc individual parameters vs age suggested no relationship between PD parameters and age (Supporting Information S6). Since age and body weight were highly correlated in the pooled population, it is likely that body weight in PK models accounted for the potential difference in PK as well as resultant PK/PD relationship between adults and paediatrics. Therefore, further age-based adjustments of cinacalcet were not warranted. Model-based simulations for paediatric patients showed that, the median starting dose suggested in the SmPC table for paediatrics <2 years, 2–6 years and 6–18 years, respectively, would provide less or similar PK exposures compared with a 30 mg dose in adults (Supporting Information S6–S7). As would be expected given the short half-life of cinacalcet, simulation results also suggested that a modest degree of accumulation upon multiple dosing would occur. Simulations of iPTH and serum cCa in the paediatric setting predicted a dose-dependent reduction in median iPTH and serum cCa. The maximum median reduction in iPTH was predicted to be <60% of baseline at the highest starting dose (10 mg), with a <5% median reduction in nadir serum cCa, with both exhibiting some degree of overlap in exposures and response across the different dose levels as a result of the estimated IIV (Supporting Information S8–S9).

At each starting dose level in paediatrics, the maximum median iPTH suppression was rapidly achieved following cinacalcet administration, with only limited fluctuations in serum cCa predicted within a dosing interval (Supporting Information S8). PK and iPTH changes reached steady-state within 1 week after treatment initiation, with serum cCa changes predicted to be stable beyond 10 days of daily dosing. Upon cessation of treatment, iPTH and cCa levels returned towards baseline. At each starting dose level, median iPTH changes from baseline fluctuated highly within a dosing interval corresponding temporally to fluctuations in drug exposures upon drug

elimination and re-administration for 4 weeks (Supporting Information S6–S10). At each starting dose level in paediatrics, there were proportions of subjects with larger cCa changes from baseline. However, even at the highest starting dose (10 mg), no subjects were predicted to have serum cCa reductions below 85% of baseline. Therefore, the starting dose suggested in the SmPC table (Supporting Information S2) is appropriate because it minimizes safety concerns associated with hypocalcaemia.

Titrated dose simulations suggested that comparable PD responses (i.e., PTH reductions ≥30% from baseline at Week 24) would occur following bi-weekly or weekly cCa monitoring and that the mean dose at Week 24 for paediatric patients would be similar. Thus, the PTH and cCa response following the more frequent cCa monitoring (weekly) was not expected to be significantly different from that following less frequent cCa monitoring (bi-weekly, as described in the SmPC). The adequacy of the proposed dose titration algorithm across all paediatric age groups in achieving desired efficacy and safety outcomes is supported by observations of fewer titration occasions in the paediatric design, smaller dose escalation steps and fewer subjects reaching maximum dose by weight.

In conclusion, a semi-physiological model has been developed incorporating key components of the PTH/Ca homeostatic system, in which cinacalcet acts through allosteric activation of the CaS receptor, in both adults and paediatric subjects with CKD and SHPT on haemodialysis. Model-based simulations implementing the titrated cinacalcet dose algorithm also demonstrated adequate PTH reductions with limited changes in serum cCa, thereby supporting the adequacy of the proposed dose titration algorithm in achieving desirable efficacy and safety balance across all paediatric groups.

ACKNOWLEDGEMENTS

COMPETING INTERESTS

P.C., W.S. and A.N. are employees of Amgen Inc. M.M., currently with Vertex Pharmaceuticals, was an employee of Amgen at the time the work was completed. P.O.G. was a consultant on this analysis.

CONTRIBUTORS

P.C., W.S., and M.M. were involved with the conception and design of the study. P.C. and A.N. were involved with patient data collection and acquisition. All authors were involved with the analysis and interpretation of data and participated in the writing and revision of the man.

REFERENCES

1. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: What's changed and why it matters. *Kidney Int*. 2017;92(1):26-36.

2. Goodman WG. The consequences of uncontrolled secondary hyperparathyroidism and its treatment in chronic kidney disease. *Semin Dial*. 2004;17(3):209-216.

3. Silver J, Naveh-Many T. Regulation of parathyroid hormone synthesis and secretion. *Semin Nephrol*. 1994;14(2):175-194.

4. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: Pathogenesis, disease progression, and therapeutic options. *Clin J Am Soc Nephrol*. 2011;6(4):913-921.

5. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med*. 2000;342(20):1478-1483.

6. Goodman WG, Quarles LD. Development and progression of secondary hyperparathyroidism in chronic kidney disease: Lessons from molecular genetics. *Kidney Int*. 2008;74(3):276-288.

7. Moe SM. Disorders involving calcium, phosphorus, and magnesium. *Prim Care*. 2008;35(2):215-237.

8. Schmitt CP, Mehls O. Mineral and bone disorders in children with chronic kidney disease. *Nat Rev Nephrol*. 2011;7(11):624-634.

9. Denburg MR, Kumar J, Jemielita T, et al. Fracture burden and risk factors in childhood CKD: Results from the CKiD cohort study. *J Am Soc Nephrol*. 2016;27(2):543-550.

10. Groothoff JW, Offringa M, Van Eck-Smit BL, et al. Severe bone disease and low bone mineral density after juvenile renal failure. *Kidney Int*. 2003;63(1):266-275.

11. Kuizon BD, Salusky IB. Growth retardation in children with chronic renal failure. *J Bone Miner Res*. 1999;14(10):1680-1690.

12. Mathias R, Salusky I, Harman W, et al. Renal bone disease in pediatric and young adult patients on hemodialysis in a children's hospital. *J Am Soc Nephrol*. 1993;3(12):1938-1946.

13. Sanchez CP. Secondary hyperparathyroidism in children with chronic renal failure: Pathogenesis and treatment. *Paediatr Drugs*. 2003;5(11):763-776.

14. Wesseling-Perry K, Pereira RC, Tseng CH, et al. Early skeletal and biochemical alterations in pediatric chronic kidney disease. *Clin J Am Soc Nephrol*. 2012;7(1):146-152.

15. Wesseling-Perry K, Salusky IB. Chronic kidney disease: Mineral and bone disorder in children. *Semin Nephrol*. 2013;33(2):169-179.

16. Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. *Physiol Rev*. 2001;81(1):239-297.

17. Nemeth EF, Scarpa A. Cytosolic Ca^{2+} and the regulation of secretion in parathyroid cells. *FEBS Lett*. 1986;203(1):15-19.

18. Nemeth EF, Steffey ME, Fox J. The parathyroid calcium receptor: a novel therapeutic target for treating hyperparathyroidism. *Pediatr Nephrol*. 1996;10(3):275-279.

19. Nemeth EF, Bennett SA. Tricking the parathyroid gland with novel calcimimetic agents. *Nephrol Dial Transplant*. 1998;13(8):1923-1925.

20. Nemeth EF, Heaton WH, Miller M, et al. Pharmacodynamics of the type II calcimimetic compound cinacalcet HCl. *J Pharmacol Exp Ther*. 2004;308(2):627-635.

21. Nemeth EF, Steffey ME, Hammerland LG, et al. Calcimimetics with potent and selective activity on the parathyroid calcium receptor. *Proc Natl Acad Sci USA*. 1998;95(7):4040-4045.

22. Levi R, Ben-Dov IZ, Lavi-Moshayoff V, et al. Increased parathyroid hormone gene expression in secondary hyperparathyroidism of experimental uremia is reversed by calcimimetics: Correlation with posttranslational modification of the trans acting factor AUF1. *J Am Soc Nephrol*. 2006;17(1):107-112.

23. Block GA, Martin KJ, de Francisco AL, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med*. 2004;350(15):1516-1525.

24. Padhi D, Harris R. Clinical pharmacokinetic and pharmacodynamic profile of cinacalcet hydrochloride. *Clin Pharmacokinet*. 2009;48(5): 303-311.

25. Padhi D, Harris RZ, Salfi M, Sullivan JT. No effect of renal function or dialysis on pharmacokinetics of cinacalcet (Sensipar/Mimpara). *Clin Pharmacokinet*. 2005;44(5):509-516.

26. Amgen Inc. Sensipar® (cinacalcet) prescribing information. 2011.

27. Amgen Inc. Sensipar® (cinacalcet) Summary of Product Characteristics. 2018.

28. Jain A, Bhayana S, Vlasschaert M, House A. A formula to predict corrected calcium in haemodialysis patients. *Nephrol Dial Transplant*. 2008;23(9):2884-2888.

29. Mouksassi MS, Marier JF, Cyran J, Vinks AA. Clinical trial simulations in pediatric patients using realistic covariates: Application to teduglutide, a glucagon-like peptide-2 analog in neonates and infants with short-bowel syndrome. *Clin Pharmacol Ther*. 2009;86(6):667-671.

30. National Center for Health Statistics. National Health and Nutrition Examination Survey 2009–2010. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2009.

31. Amgen Inc. Clinical Study Report: A phase 3 study to assess the efficacy and safety of an oral calcimimetic agent (AMG 073) in secondary hyperparathyroidism of end stage renal disease treated with hemodialysis. 2003.

32. Amgen Inc. Clinical Study Report: A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet HCl in pediatric subjects with chronic kidney disease and secondary hyperparathyroidism receiving dialysis. 2016.

33. Joborn H, Hjemdahl P, Wide L, Akerström G, Ljunghall S. Reduction of serum parathyroid hormone levels during sympathetic stimulation in man. *J Endocrinol Invest*. 1987;10(2):153-156.

34. Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucleic Acids Res*. 2018;46(D1):D1091-D1106.

35. Alexander SPH, Christopoulos A, Davenport AP, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: G protein-coupled receptors. *Br J Pharmacol*. 2017;174(Suppl 1):S17-S129.

36. Chattopadhyay N. Biochemistry, physiology and pathophysiology of the extracellular calcium-sensing receptor. *Int J Biochem Cell Biol*. 2000;32(8):789-804.

37. Ehlert FJ. Estimation of the affinities of allosteric ligands using radioligand binding and pharmacological null methods. *Mol Pharmacol*. 1988;33(2):187-194.

38. Black JW, Leff P. Operational models of pharmacological agonism. *Proc R Soc Lond B Biol Sci*. 1983;220(1219):141-162.

39. Peterson MC, Riggs MM. A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. *Bone*. 2010;46(1):49-63.

40. Walter S, Baruch A, Dong J, et al. Pharmacology of AMG 416 (velcalcetide), a novel peptide agonist of the calcium-sensing receptor, for the treatment of secondary hyperparathyroidism in hemodialysis patients. *J Pharmacol Exp Ther*. 2013;346(2):229-240.

41. Standing JF. Understanding and applying pharmacometric modelling and simulation in clinical practice and research. *Br J Clin Pharmacol*. 2017;83(2):247-254.

42. Chen P, Olsson Gisleskog P, Perez-Ruixo JJ, et al. Population pharmacokinetics and pharmacodynamics of the calcimimetic etelcalcetide in chronic kidney disease and secondary hyperparathyroidism receiving hemodialysis. *CPT Pharmacometrics Syst Pharmacol*. 2016;5(9):484-494.

43. Wang B, Ludden T, Gonzalez M, Rein P, Harris R. A population pharmacokinetic (PK) and pharmacodynamic (PD) analysis of cinacalcet HCl in renal-dialysis patients with secondary hyperparathyroidism (HPT). *Clin Pharmacol Ther*. 2004;75:62.

44. Mahmood I. Dosing in children: A critical review of the pharmacokinetic allometric scaling and modelling approaches in paediatric drug development and clinical settings. *Clin Pharmacokinet*. 2014;53(4): 327-346.

45. Raposo JF, Sobrinho LG, Ferreira HG. A minimal mathematical model of calcium homeostasis. *J Clin Endocrinol Metab*. 2002;87(9): 4330-4340.

46. Riggs MM, Peterson MC, Gastonguay MR. Multiscale physiology-based modeling of mineral bone disorder in patients with impaired kidney function. *J Clin Pharmacol*. 2012;52(S1):45s-53s.

47. Abraham AK, Mager DE, Gao X, Li M, Healy DR, Maurer TS. Mechanism-based pharmacokinetic/pharmacodynamic model of parathyroid hormone-calcium homeostasis in rats and humans. *J Pharmacol Exp Ther*. 2009;330(1):169-178.

48. Lalonde RL, Gaudreault J, Karhu DA, Marriott TB. Mixed-effects modeling of the pharmacodynamic response to the calcimimetic agent R-568. *Clin Pharmacol Ther*. 1999;65(1):40-49.

49. Abraham AK, Maurer TS, Kalgutkar AS, et al. Pharmacodynamic model of parathyroid hormone modulation by a negative allosteric modulator of the calcium-sensing receptor. *AAPS J*. 2011;13(2):265-273.

50. Chen P, Narayanan A, Wu B, et al. Population pharmacokinetic and pharmacodynamic modeling of etelcalcetide in patients with chronic kidney disease and secondary hyperparathyroidism receiving hemodialysis. *Clin Pharmacokinet*. 2018;57(1):71-85.

51. Jong G. Pediatric development: Physiology, enzymes, drug metabolism, pharmacokinetics and pharmacodynamics. In: Bar-Shalom D, Rose K, eds. *Pediatric Formulations: A Roadmap. AAPS Advances in the Pharmaceutical Sciences Series 11*. New York: Springer; 2014.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.