

ARTICLE OPEN ACCESS

Population Pharmacokinetics Modeling of Selpercatinib to Support Posology in Pediatric Patients With RET-Altered Metastatic Thyroid Cancer or Solid Tumors

Dan Liu¹ | Jan-Stefan van der Walt² 

¹Global PKPD and Pharmacometrics, Eli Lilly and Company, UK | ²Occams Coöperatie U.A, the Netherlands

Correspondence: Dan Liu (liu_dan1@lilly.com)

Received: 21 November 2024 | **Revised:** 31 March 2025 | **Accepted:** 25 April 2025

Funding: The work was supported by Loxo Oncology, a wholly owned subsidiary of Eli Lilly.

Keywords: exposure matching | pediatric posology | population pharmacokinetics | RET-altered cancer | selpercatinib

ABSTRACT

Selpercatinib is a first-in-class, highly selective, RET kinase inhibitor with CNS activity, approved for the treatment of RET-altered lung, thyroid, and other cancers. We report pharmacokinetic analyses to identify factors affecting selpercatinib steady-state exposure and support posology in pediatric patients. Population pharmacokinetic analyses using nonlinear mixed-effects modeling were performed on data from two ongoing, open-label, Phase 1/2 studies in adult and pediatric patients with advanced solid tumors. In LIBRETTO-001 (NCT03157128) patients (≥ 12 years) received oral selpercatinib from 20 mg once daily through 240 mg twice daily (BID) during phase 1 and 160 mg BID in phase 2. In LIBRETTO-121 (NCT03899792), patients (6 months–21 years) received doses based on body surface area (BSA), starting at a dose expected to match adult exposure of 160 mg BID. Overall, 8024 selpercatinib plasma concentration measurements from 830 patients were included in the pharmacokinetic analysis. The final model, a 2-compartment disposition model with sequential zero- and first-order absorption, was similar to a previously developed adult model, which identified weight, dose, and Asian race as covariates. Simulations performed using the final model suggested the following dose regimen as appropriate for patients aged 2–17 years: 40 mg three times a day for pediatric patients with a BSA of 0.33–0.65 m²; BSA-based dosing (92 mg/m² rounded for 40 and 80 mg capsules) for pediatric patients 2 to < 12 years, and BSA ≥ 0.66 m²; and weight-based dosing (120 mg BID < 50 kg and 160 mg BID ≥ 50 kg) for adolescent patients ≥ 12 years.

JEL Classification: Pediatric Rare Disease

1 | Introduction

Selpercatinib is a first-in-class, highly selective, small molecule inhibitor of the rearranged during transfection (RET)-selective tyrosine kinase [1]. Alterations in the *RET* gene, including fusions and point mutations, can lead to constitutive activation of RET signaling that has been observed in patients with thyroid

and non-small-cell lung cancer (NSCLC) as well as in other tumor types [2, 3].

Selpercatinib was initially approved for use by the United States Food and Drug Administration (FDA) for thyroid cancer indications in adults and pediatric patients 12 years of age and older [4]. It also was previously granted accelerated approval for RET

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2025 The Author(s). *CPT: Pharmacometrics & Systems Pharmacology* published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics.

Summary

- What is the current knowledge on the topic?
 - Selpercatinib is a small molecule inhibitor of the RET receptor tyrosine kinase that has been approved for the treatment of patients with RET-altered lung, thyroid, and other solid tumors.
- What question did this study address?
 - We developed an updated population pharmacokinetic model for selpercatinib based on data from both children and adults, which was further used to support selpercatinib pediatric posology for children aged 2–17 years.
- What does this study add to our knowledge?
 - We matched selpercatinib exposure in children to the exposure observed in adults to determine the optimal doses for children with an activating RET alteration and an advanced solid or primary central nervous system tumor.
- How might this change drug discovery, development, and/or therapeutics?
 - The proposed dose regimen for children aged 2–17 years has been approved by the US Food and Drug Administration and is anticipated to provide sufficient exposure to children in a range that is pharmacologically active and safe.

fusion-positive NSCLC and other solid tumors in adults [5]. The approved dose regimen for adults is adapted flat dosing based on body weight (120 mg twice daily [BID] for less than 50 kg and 160 mg BID for 50 kg or greater).

The FDA recently granted accelerated approval to selpercatinib (Retevmo, Eli Lilly and Company) for pediatric patients 2 years of age and older on 29 May 2024 [6] with the following: advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, who require systemic therapy; advanced or metastatic thyroid cancer with a *RET* gene fusion, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate); and locally advanced or metastatic solid tumors with a *RET* gene fusion, that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options, all of which were detected by an FDA-approved test.

This is the first FDA approval of a targeted therapy for pediatric patients younger than 12 years of age with *RET* alterations [6]. In the ongoing pediatric study (LIBRETTO-121), patients were treated using body surface area (BSA)-based dosing (92 mg/m² BID not to exceed 160 mg BID) [7]. The appropriateness of the 92 mg/m² dose in pediatric patients was supported by interim pharmacokinetic (PK) data from LIBRETTO-121, which suggested that the dose of 92 mg/m² BID (up to a maximum of 160 mg BID) resulted in a similar steady-state exposure in pediatric patients as in adult patients with cancer treated with 160 mg BID. The goal of this analysis was to explore pediatric posology based on modeling, simulation, and exposure matching between pediatric and adult patients.

2 | Methods

2.1 | Study Design

The population PK analysis used data from LIBRETTO-001 (NCT03157128) and LIBRETTO-121 (NCT03899792), two ongoing, multicenter, open-label Phase 1/2 studies of selpercatinib in patients with *RET*-altered solid tumors. The data cut-off date was January 13, 2023 for both studies.

Details of LIBRETTO-001 have been reported previously [1, 8]. Briefly, eligible patients were adults and adolescents (aged ≥ 18 years; or ≥ 12 years, where allowed by regulatory authorities) diagnosed with an advanced or metastatic solid tumor. In the phase 1 dose escalation portion of LIBRETTO-001, patients received selpercatinib at doses ranging from 20 mg once daily through 240 mg BID. In phase 2, all patients received the recommended dose of 160 mg BID [9].

LIBRETTO-121 is a study of selpercatinib in pediatric participants (allowed enrollment age from ≥ 6 months to ≤ 21 years) with an activating *RET* alteration and an advanced solid or primary central nervous system tumor. In phase 1, participants were enrolled using a rolling 6-dose escalation scheme in which the starting dose of selpercatinib was equivalent to the adult recommended phase 2 dose (RP2D) of 160 mg BID. Once the maximum tolerated dose (MTD) and/or RP2D were identified, participants were enrolled in one of four phase 2 dose expansion cohorts depending on tumor histology and genotype.

The LIBRETTO-001 and LIBRETTO-121 trials were conducted in accordance with Good Clinical Practice guidelines, in line with the principles of the Declaration of Helsinki, and all applicable country and local regulations. The protocols were approved by the institutional review board or independent ethics committee at each investigative site. Written informed consent was provided by all adult participants and by the parents or legal guardians of pediatric participants.

2.2 | Sample Collection and Analysis

In both trials, selpercatinib was administered orally in a continuous 28-day cycle until disease progression, death, unacceptable toxicity, or another reason for treatment discontinuation. In LIBRETTO-001, blood for plasma PK assessment was collected at up to 1 h predose and at 1, 2, 4 h (± 15 min) and 8 h (± 30 min) postdose on Cycle (C) 1 Day (D) 8 (C1D8). In some cases, blood was also collected for plasma PK assessment on C1D1, C3D1, C5D1, and Day 8 of a patient's new dose (inpatient dose escalation). Additional PK sampling was also performed in patients when considered necessary by the investigator to understand exposure in relation to possible safety or efficacy findings or if there was a change to the selpercatinib formulation being administered.

In LIBRETTO-121, blood for plasma PK assessment was collected at 2 and 4 h (± 15 min) postdose on C1D1, and at up to 1 h predose, and at 1, 2, 4 h (± 15 min), and 8 h (± 30 min) postdose

on C1D8 and C3D1 or during inpatient dose escalation. Missing dosing times were imputed for 2 patients.

Plasma concentrations of selpercatinib were determined using a validated bioanalytical assay with a lower limit of quantification of 1 ng/mL. Data below the quantifiable limit (BQL) were excluded from analysis. Furthermore, no data outliers that warranted exclusion were observed.

2.3 | Population PK Analysis

A previously developed adult population PK model [10] was updated based on the combined data from LIBRETTO-001 and LIBRETTO-121 trials. The adult model was a 2-compartment disposition model with sequential zero- and first-order absorption. Interindividual variability terms were included on apparent clearance (CL), apparent central volume of distribution (Vc), first-order absorption rate constant (Ka), and duration of zero-order absorption (D1). Body weight was included following allometric principles with fixed exponents of 0.75 for CL and intercompartmental clearance (Q) and 1.0 for Vc and peripheral volume of distribution (Vp).

A new covariate analysis was performed on the updated population PK model to incorporate characteristics of the target pediatric population and identify factors influencing selpercatinib PK variability. The explored covariates include baseline weight, baseline age, race (Asian vs. non-Asian), selpercatinib dose, sex, baseline creatinine clearance, liver function tests (alanine

transaminase, aspartate aminotransferase, and total bilirubin), and concomitant medication. The concomitant use of CYP3A4 inhibitors and inducers, and antacids (H2 receptor antagonists [H2-blockers] and/or proton pump inhibitors [PPIs]), was absent in LIBRETTO-121 (only 1 patient used an H2-blocker), whereas in LIBRETTO-001, 34% of patients used concomitant CYP3A4 inhibitors, and 46% used either PPIs or H2-blockers (Table S1). The model explored concomitant medication covariate as categorical variables. All tested covariates have been provided in Table S2. The base model for covariate analysis of the combined adult and pediatric data included body weight effects: body weight was normalized to 70 kg with exponents fixed at 0.75 (CL/F and Q/F) or 1 (Vc/F and Vp/F). The relationship between dose and CL/F was modeled as a time-varying continuous covariate to account for any dose reductions or increases. Automated stepwise covariate modeling (SCM) using a forward addition/backward deletion procedure was used. Forward covariate inclusion (p value < 0.05) and backward deletion (p value < 0.001) was followed by model reduction to refine the model. Models were evaluated using standard goodness-of-fit plots and prediction-corrected visual predictive checks (pcVPCs).

2.4 | Simulations

Since LIBRETTO-121 allowed patients to be enrolled from the age of 6 months, simulations were performed for children aged 6 months (lowest allowed enrollment age) to < 18 years from the National Health and Nutrition Examination Survey (NHANES) Dual Energy X-ray Absorptiometry (DXA)

TABLE 1 | Summary of baseline demographics.

Population characteristics	LIBRETTO-001	LIBRETTO-121	Total
Sex			
Male, n (%)	411 (51.2)	16 (59.3)	427 (51.4)
Female, n (%)	392 (48.8)	11 (40.7)	403 (48.6)
Age, years			
Mean (SD)	57.4 (14.1)	13.4 (4.8)	56.0 (15.9)
Median (range)	59.0 (15.0–92.0)	14.0 (2.0–20.0)	58.0 (2.0–92.0)
Age group			
< 12 years, n (%)	0 (0.0)	6 (22.2)	6 (0.7)
≥ 12 to < 18 years, n (%)	3 (0.4)	15 (55.6)	18 (2.2)
≥ 18 years, n (%)	800 (99.6)	6 (22.2)	806 (97.1)
Weight, kg			
Mean (SD)	71.0 (19.6)	48.3 (20.7)	70.3 (20.0)
Median (range)	67.3 (26.8–179)	48.5 (9.6–97.7)	67.0 (9.6–179)
BSA ^a , m ²			
Mean (SD)	1.80 (0.258)	1.43 (0.417)	1.78 (0.273)
Median (range)	1.77 (1.11–2.79)	1.47 (0.446–2.21)	1.76 (0.4462.79)

Note: Values were rounded to 3 significant digits. Categorical values are shown as number of subjects (%).

Abbreviations: BSA, body surface area; SD, standard deviation.

^aNumber missing 22/803 in the LIBRETTO-001.

database [11] to predict selpercatinib exposure. Considering that selpercatinib is mainly metabolized by CYP3A4, which matures around 2 years of age [12], the simulations for selpercatinib concentrations for pediatric patients aged 6 months to 2 years old should be interpreted with caution, as the model may overpredict concentrations in these very young patients (<2 years of age). Furthermore, as of the data cut for this analysis, there were no patients aged <2 years in LIBRETTO-121 (Table 1). Therefore, the pediatric posology will be mainly informed based on simulations for pediatric patients aged 2–17 years.

The maximum concentration (C_{max}) and area under the curve over two dosing intervals (AUC_{0-24}) on C1D8 were simulated and evaluated for three dosing regimens:

- the dosing used in LIBRETTO-121, that is, BSA-based dosing (92 mg/m^2 rounded for 40 and 80 mg capsules),
- adapted flat dosing (120 mg BID for weight < 50 kg and 160 mg BID for weight ≥ 50 kg)
- 40 mg three times a day (TID) for pediatric patients with BSA from 0.33 to 0.65 m^2 ; BSA-based dosing (92 mg/m^2 rounded for 40 and 80 mg capsules) for pediatric patients 2 to <12 years and BSA $\geq 0.66 \text{ m}^2$; and weight-based dosing (120 mg BID < 50 kg and 160 mg BID ≥ 50 kg) for adolescent patients aged ≥ 12 years.

The simulated selpercatinib exposures in children were compared across age and weight ranges to the exposure observed in adult patients with cancer treated with 160 mg BID. BSA was determined using the method described by Mosteller [13].

2.5 | Software Details

The population analyses and simulations were performed using the nonlinear mixed-effects modeling software (NONMEM; version 7.5.0), using the first-order conditional estimation (FOCE) estimation method with interaction, supplemented with Perl-speaks-NONMEM (PsN), version 5.3.0 [14, 15]. Covariate relationships were assessed using stepwise covariate model

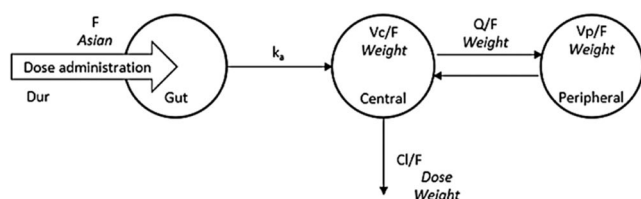


FIGURE 1 | Schematic view of the final population pharmacokinetic model. Note: Text in *italics* is the covariate associated with the adjacent pharmacokinetic parameter. Abbreviations: Cl/F, apparent clearance; Dur, duration of zero-order absorption; F, bioavailability (fixed to 100%); Gut, gastrointestinal tract; k_a , first-order absorption rate constant; Q/F, apparent intercompartmental clearance; Vc/F, apparent volume of distribution for the central compartment; Vp/F, apparent volume of distribution of the peripheral compartment.

building (PsN, version 5.3.0). R software version 4.2.1 (2022-06-23 ucrt; 64-bit; R Development Core Team, <http://www.r-project.org>) [16] was used for general scripting, running simulations, data management, goodness-of-fit (GOF) analyses, and model evaluation.

3 | Results

3.1 | Demographic and Baseline Characteristics

Summaries of demographics are provided in Table 1. Overall, 803 patients from LIBRETTO-001 (median age, 59.0 years; range, 15–92 years) and 27 patients from LIBRETTO-121 (median age, 14.0 years; range, 2–20 years) were included in the analysis. The analysis used a total of 8024 selpercatinib concentration–time data points (7723 from LIBRETTO-001 and

TABLE 2 | NONMEM parameter estimates for the final model.

Parameter	Estimate (95% CI)	IIV	Shrinkage ^a
CL (L/h)	6.04 (5.79/6.29)	48.8%	3.5%
Vc (L)	99.6 (86.3/113)	66.1%	32.0%
Vp (L)	91.3 (82.9/99.7)		
k_a (1/h)	1.47 (1.25/1.69)	63.6%	57.8%
Q (L/h)	29.6 (24.2/35.0)		
F1 (fraction)	1.00 Fixed		
Dur (h)	1.09 (1.05/1.13)	56.2%	49.2%
Dose effect on CL (%/mg)	−0.321 (−0.439/−0.203)		
Asian race effect on F1 (%)	18.3 (10.9/25.8)		
Additive RUV (mg/L)	61.5 (37.4/85.6)		8.7%
Proportional RUV (fraction)	0.253 (0.231/0.275)		8.7%

Functions and Parameters Used to Test Covariates

$$CL = \theta_{CL} * (1 + \theta_{Dose\ effect\ on\ CL} * (Dose - 160mg)) * \left(\frac{Weight}{70kg}\right)^{0.75}$$

$$F1 = \theta_{F1} * (1 + \theta_{Asian\ race\ effect\ on\ F1})$$

$$Vc = \theta_{Vc} * \left(\frac{Weight}{70\ kg}\right)^{1.0}$$

$$Vp = \theta_{Vp} * \left(\frac{Weight}{70\ kg}\right)^{1.0}$$

$$Q = \theta_Q * \left(\frac{Weight}{70\ kg}\right)^{0.75}$$

where θ_{PAR} is the population estimate of parameter (PAR)

Abbreviations: CL, apparent clearance; Dur, duration of zero-order absorption; F1, relative bioavailability; IIV, interindividual variability; k_a , first-order absorption rate constant; NONMEM, nonlinear mixed-effects modeling software; Q, intercompartmental clearance; RUV, residual unexplained variability; Vc, apparent central volume of distribution; Vp, peripheral volume of distribution.

^aShrinkage calculated using the standard deviation.

301 from LIBRETTO-121) from 830 patients. A total of 133 concentrations were BQL and excluded (131 concentrations from 101 patients in LIBRETTO-001 and 2 concentrations from 1 patient in LIBRETTO-121). The number of patients in each starting dosing stratum is summarized in Table S3. For patients under 12 years old, 6 patients provided 59 concentration data points to support the model development.

3.2 | PK Analyses

The PK of selpercatinib in pediatric, adolescent, and adult patients from LIBRETTO-001 and LIBRETTO-121 trials was jointly described using an updated population PK model (Figure 1). The final model is a 2-compartment disposition model with sequential zero- and first-order absorption. The final model was similar to the previously developed adult model [10] including weight, dose, and Asian race as statistically significant covariates (Table 2).

TABLE 3 | Recommended selpercatinib doses for patients aged 2–17 years.

Population	Dose
12 years of age or older (dose based on body weight)	
< 50 kg	120 mg BID
≥ 50 kg	160 mg BID
2 to < 12 years of age (dose based on body surface area)	
0.33–0.65 m ^{2a}	40 mg TID
0.66–1.08 m ^{2a}	80 mg BID
1.09–1.52 m ^{2a}	120 mg BID
≥ 1.53 m ^{2a}	160 mg BID

Note: Dosing pediatric patients with a body surface area less than 0.33 m² is not recommended.
Abbreviations: BID, twice daily; TID, 3 times a day.
^a92 mg/m² rounded for 40 and 80 mg capsules.

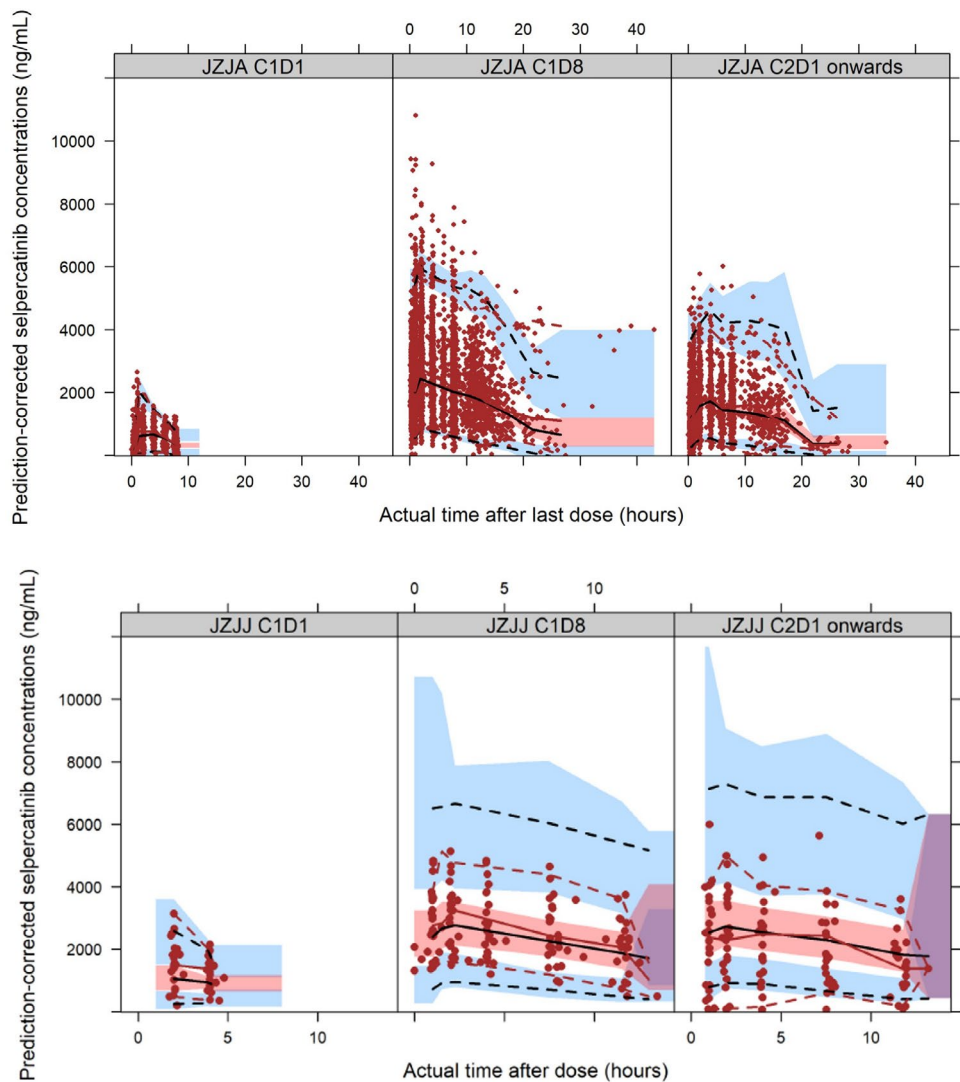


FIGURE 2 | Prediction-corrected visual predictive check with observed data for pediatric subjects in LIBRETTO-001 and LIBRETTO-121 studies, stratified by visit. Note: The lines are the 2.5th, 50th, and 97.5th percentiles of the prediction-corrected observed data (red) and the prediction-corrected simulated data (black). The red dots are the prediction-corrected observed data. The shaded areas are the 95% confidence intervals for the 2.5th, 50th, and 97.5th percentiles, respectively. Abbreviations: C1D1, Cycle 1 Day 1; C1D8, Cycle 1 Day 8; JZJA, LIBRETTO-001; JZJJ, LIBRETTO-121.

The final model, similar to the model previously developed for adults, maintained the standard allometric scaling coefficients for weight, CL, Vc, Vp, and Q, and included the covariate effects of dose on CL/F and Asian race on bioavailability.

The adequacy of the final model was evaluated using pcVPCs [17] (Figure 2) and goodness-of-fit plots (Figures S1 and S2). The final population PK model was used to simulate 1000 replicates of the analysis dataset. The pcVPCs were conditioned on the study (LIBRETTO-001 or LIBRETTO-121) and time of PK samples collection (C1D1, C1D8, or C2 onward). The C1D8 and C2D1 onward data were considered the most important data to assess the predictive performance of the model for simulating selpercatinib exposures in children considering pediatric and adolescent patients will be on chronic treatment. The central tendency in the data (solid red line) was well captured by the simulated data (red area). Importantly, for C1D8 and C2D1 onward data in LIBRETTO-121, the 2.5th and 97.5th percentiles of the observed data (red dashed lines) were within the 95% confidence interval of the simulated data (blue areas) (Figure 2).

Random effect plots for ETA clearance vs. starting dose was also provided in Figure S3. Additionally, pcVPCs of concentrations versus WT and age were provided in Figures S4 and S5 for pediatric and adolescent patients from study LIBRETTO-121. The effect of dose on CL/F appears adequately covered. Body weight effects were predefined and included in the model on clearances and volumes of distribution (Table 2). The age effect appeared to be driven by older adults (Figure S3), with no obvious effect on younger individuals. The inclusion of an age effect in CL/F resulted in an increase in the typical value of CL/F from 5.94 (95% CI: 5.73–6.15) L/h in the base model to 7.30 (95% CI: 6.73–7.88) L/h in the SCM final backward model. Due to the faster clearance introduced by the age effect, the model underpredicted the selpercatinib concentration–time profiles during C1D8 in patients in study LIBRETTO-121. With limited data in very young children, the clinical relevance of the age effect on CL/F is unknown. Therefore, the age effect was removed during the model refinement and not retained in the final model. Although the final model did not include an age effect on CL/F, it described well the C1D8 and C2D1 onward steady state pediatric and adolescent PK data from study LIBRETTO-121 (Figure 2). Overall, the final model described the combined adult and pediatric data well and demonstrated good predictive performance.

Based on the final model, simulations were performed based on children sampled from the NHANES database. Adolescent patients aged 12 years or older (average BSA $\approx 1.69 \text{ m}^2$) with BSA-based dosing of 92 mg/m^2 BID are likely to have an actual administered dose range from 120 to 160 mg BID, in line with adult weight-based dosing (120 mg BID in patients $< 50 \text{ kg}$ and 160 mg BID in patients $\geq 50 \text{ kg}$). Therefore, for adolescent patients aged 12 years or older, weight-based dosing (120 mg BID in patients $< 50 \text{ kg}$ and 160 mg BID in patients $\geq 50 \text{ kg}$) was used in the simulations to explore whether it could provide exposure in adolescent patients matching that of adults.

Simulations indicated that adapted flat dosing-matched adult exposure for children aged 12 years and older, but not for younger children whose C_{max} and AUC_{0-24} values on C1D8 would exceed

the exposure observed in adult patients with cancer treated with 160 mg BID (Figure 3).

BSA-based dosing (92 mg/m^2 rounded for 40 and 80 mg capsules) would provide exposure (C_{max} and AUC_{0-24}) generally matching the exposure in adults with cancer dosed with 160 mg BID (Figure 3). However, for very young children aged approximately 2–3 years, the BSA-based dosing (92 mg/m^2 rounded for 40 and 80 mg capsules) would provide slightly lower exposure compared with adults (Figure 3). After adjusting the dose for those very young pediatric patients using BSA, the modified dose regimen (Table 3) would provide exposure for patients aged 2–17 years matching that of adults (Figure 4), suggesting that this regimen is appropriate for adolescent and pediatric patients aged 2–17 years.

4 | Discussion

The PK of selpercatinib in children and adults from LIBRETTO-001 and LIBRETTO-121 trials was adequately described using an updated population PK model. A therapeutic range for efficacy and safety has not been established for selpercatinib; therefore, pediatric posology aimed to match selpercatinib exposure in children to the exposure observed in adult patients with cancer treated with 160 mg BID.

Model development relied on limited pediatric PK data from very young patients. There were only 6 patients under 12 years of age with 59 concentration data points used to support the model development. Although the final model captured those data reasonably (Figure 2), it should be interpreted with caution due to the small sample size for very young patients.

Based on the pooled data from study LIBRETTO-121 and LIBRETTO-001, automated SCM retained three covariate effects following deletion ($p < 0.001$): Age effect on CL/F, Dose effect on CL/F, and Asian race effect on F1. The age effect seemed to be primarily influenced by older ages (Figure S3) in the adult data, with no significant effect observed for younger ages. Incorporating an age effect on clearance could result in biased population predictions in children. The effect of age on clearance was also reassessed using the final model. This was done by introducing a relationship between clearance and age using a linear model (a “proportional change model” centered on the median age of 58 years) or a segmented linear model (a “hockey stick” model with break point set to the median age of 58 years):

$$CL_i = \theta_{CL} * \text{age}_{\text{effect}} * (1 + \theta_{\text{Dose effect on CL}} * (\text{Dose} - 160 \text{ mg})) * \left(\frac{\text{Weight}_i}{70 \text{ kg}} \right)^{0.75}$$

Linear model:

$$\text{age}_{\text{effect}} = (1 + \theta_{\text{age_effect}} * (\text{age} - 58 \text{ years}))$$

Segmented linear model:

$$\text{if age} \leq 58 \text{ years: } \text{age}_{\text{effect}} = (1 + \theta_{\text{age_effect1}} * (\text{age} - 58 \text{ years}))$$

$$\text{if age} > 58 \text{ years: } \text{age}_{\text{effect}} = (1 + \theta_{\text{age_effect2}} * (\text{age} - 58 \text{ years}))$$

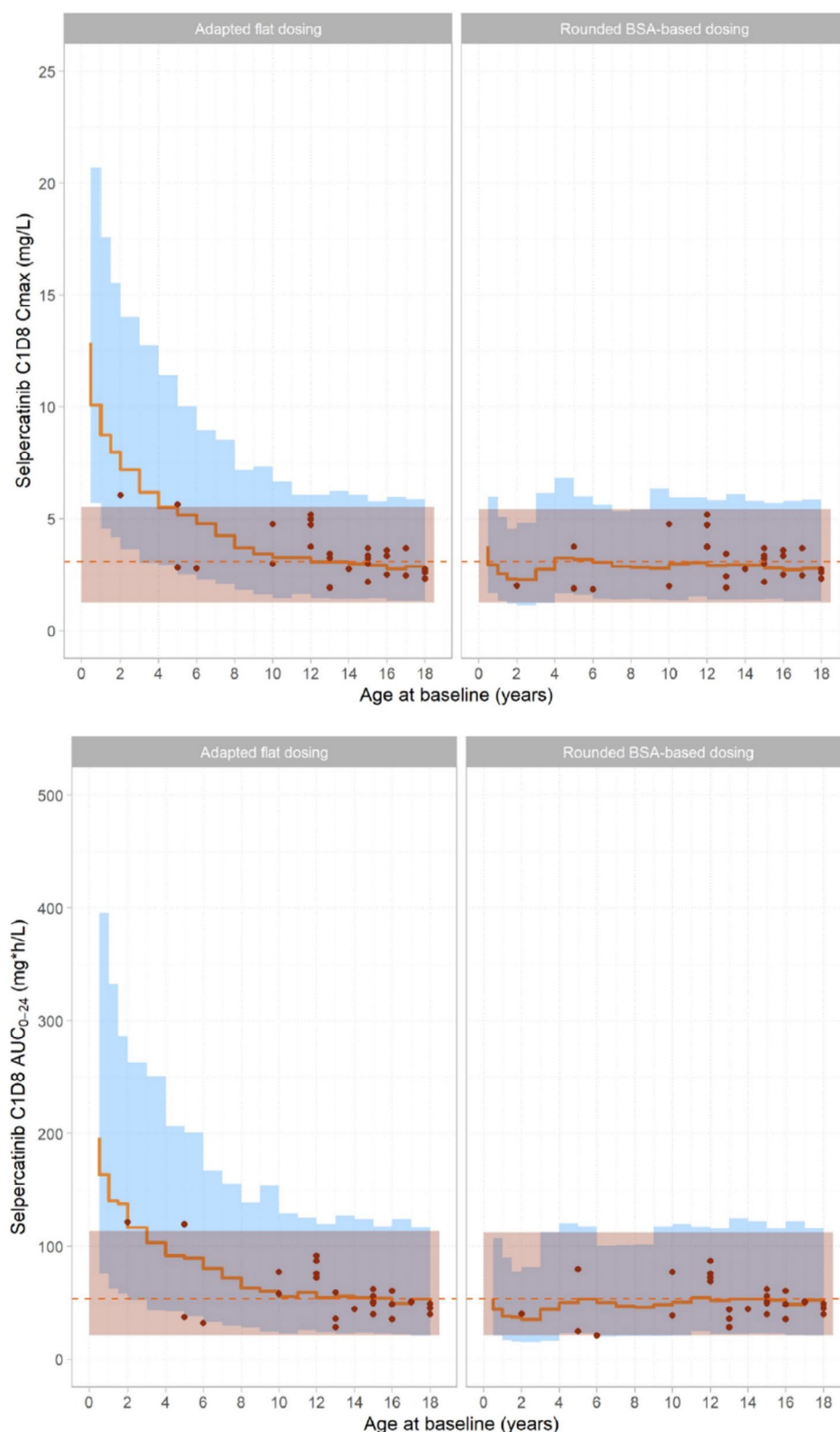


FIGURE 3 | Simulated selpercatinib Cycle 1 Day 8 C_{max} and AUC_{0-24} by age and body weight for the final model based on the recommended dose regimens in Table 3 and patients sampled from the NHANES database. *Note:* Adapted flat dosing: Weight-based dosing (120 mg BID < 50 kg and 160 mg BID $\geq$ 50 kg); rounded body surface area-based dosing: 92 mg/m² rounded for 40 and 80 mg capsules. Orange line and blue area: Median and 90% of simulated values for children sampled from the NHANES database. Red dots: Individual predicted values using empirical Bayes estimates from the final population pharmacokinetics model and using the indicated dosing regimen. Adult reference ranges are presented as orange-colored areas in the background corresponding to 90% of simulated values sampled from the NHANES database using the indicated dosing regimen. Orange dashed line: Adult reference level. Abbreviations: AUC_{0-24} , area under the curve over two dosing intervals; BID, twice daily; C1D8, Cycle 1 Day 8; C_{max} , maximum concentration; NHANES, National Health and Nutrition Examination Survey.

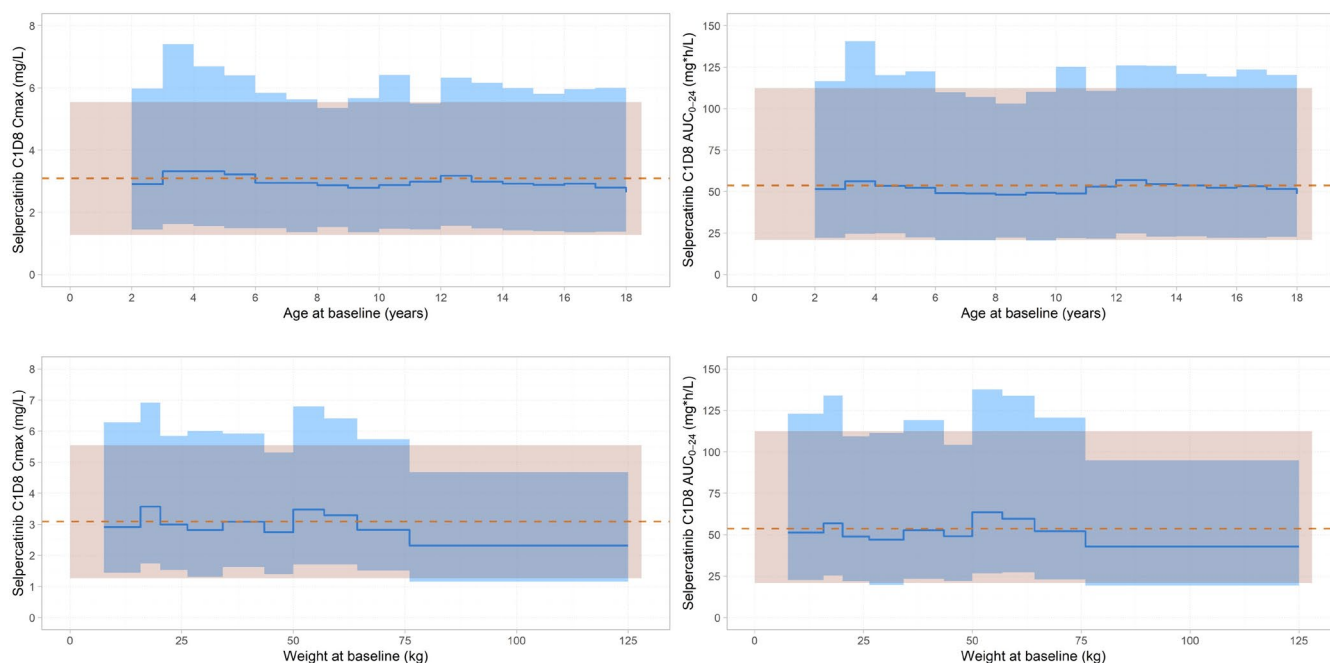


FIGURE 4 | Simulated Cycle 1 Day 8 C_{max} and AUC_{0-24} by age and body weight for the final model based on the recommended dose regimens in Table 3. Note: Blue solid line and blue area: Median and 90% of simulated values for children sampled from the NHANES database. Adult reference ranges are presented as orange-colored areas in the background corresponding to 90% of simulated values sampled from the NHANES database. Orange dashed line: Adult reference level. Abbreviations: AUC_{0-24} , area under the concentration–time curve over two dosing intervals; C1D8, Cycle 1 Day 8; C_{max} , maximum concentration; NHANES, National Health and Nutrition Examination Survey.

where CL_i is individual-specific realizations of CL/F for the i th subject, and θ_{CL} is the typical value of CL/F . $\theta_{Dose\ effect\ on\ CL}$ and $\theta_{age\ effect}$ are covariate effects of dose and age on clearance, respectively.

The addition of age as a covariate on CL/F decreased the objective function value (OFV) by -43.998 points for the linear model and by -49.995 points for the segmented linear model compared with the final model, respectively. However, both models with age as a covariate on clearance resulted in biased population predictions in children (Study LIBRETTO-121) as shown in the goodness-of-fit plot (Figure S6) and underpredicted the selpercatinib concentration–time profiles on C1D8 as shown in the pcVPC (Figure S7). The age effect was then removed during the model refinement. The final model without age effect on CL/F described well the C1D8 and C2D1 onward steady state PK data from pediatric and adolescent patients in study LIBRETTO-121 (Figure 2).

Based on the final model, simulations (Figure 4) suggest that the proposed dose regimen (Table 3) is considered appropriate for patients aged 2–17 years, as it is predicted to provide selpercatinib systemic exposures (AUC_{0-24} and C_{max}) matching the exposure in adult cancer patients dosed with selpercatinib 160 mg BID: 40 mg TID for pediatric patients with BSA from 0.33 to 0.65 m²; BSA-based dosing (92 mg/m² rounded for 40 and 80 mg capsules) for pediatric patients aged 2 to <12 years and BSA ≥ 0.66 m²; and weight-based dosing (120 mg BID <50 kg and 160 mg BID ≥ 50 kg) for adolescent patients aged ≥ 12 years.

Additionally, simulations were mainly performed for children sampled from the NHANES database aged 6 months to 17 years.

Considering selpercatinib is predominantly metabolized by *CYP3A4*, which matures at around 2 years of age [12], the simulations for pediatric patients aged 6 months to 2 years old should be interpreted with caution, as the model may overpredict concentrations in these very young patients (<2 years of age).

5 | Conclusions

The PK of selpercatinib in children and adults from LIBRETTO-121 and LIBRETTO-001 trials was jointly described using an updated population PK model. The final model was similar to the previously developed adult model, which identified weight, dose, and Asian race as important covariates. Simulations were performed based on the final model and supported the following pediatric posology for children aged 2–17 years, that is, 40 mg TID for pediatric patients with BSA from 0.33 to 0.65 m²; BSA-based dosing (92 mg/m² rounded for 40 and 80 mg capsules) for pediatric patients aged 2 to <12 years and BSA ≥ 0.66 m²; and weight-based dosing (120 mg BID <50 kg and 160 mg BID ≥ 50 kg) for adolescent patients aged ≥ 12 years.

Author Contributions

D.L. and J.S.V. wrote the manuscript, designed research, analyzed data, and interpreted results.

Acknowledgments

We thank the patients and their families and caregivers, as well as the investigators and their personnel for their participation in the LIBRETTO-1 and LIBRETTO-121 trials. Medical writing support was

provided by Anchal Sood of Syneos Health and funded by Eli Lilly and Company in accordance with Good Publication Practice (2022) guidelines (<https://www.ismpp.org/gpp-2022>). Some results from this study were published as a Congress abstract at PAGE 2024. Reference: PAGE 32 (2024) Abstr 11052 [www.page-meeting.org/?abstract=11052].

Conflicts of Interest

D. Liu is an employee and shareholder of Eli Lilly and Company. Jan-Stefan van der Walt was previously employed by Eli Lilly and Company and is a shareholder of Eli Lilly and Company.

References

1. V. Subbiah, J. Wolf, B. Konda, et al., "Tumour-Agnostic Efficacy and Safety of Selpercatinib in Patients With RET Fusion-Positive Solid Tumours Other Than Lung or Thyroid Tumours (LIBRETTO-001): A Phase 1/2, Open-Label, Basket Trial," *Lancet Oncology* 23, no. 10 (2022): 1261–1273, [https://doi.org/10.1016/S1470-2045\(22\)00541-1](https://doi.org/10.1016/S1470-2045(22)00541-1).
2. A. Desilets, M. Repetto, S. R. Yang, E. J. Sherman, and A. Drilon, "RET-Altered Cancers—A Tumor-Agnostic Review of Biology, Diagnosis and Targeted Therapy Activity," *Cancers (Basel)* 15, no. 16 (2023): 4146, <https://doi.org/10.3390/cancers15164146>.
3. A. T. Regua, M. Najjar, and H. W. Lo, "RET Signaling Pathway and RET Inhibitors in Human Cancer," *Frontiers in Oncology* 12 (2022): 932353, <https://doi.org/10.3389/fonc.2022.932353>.
4. "FDA Approves Selpercatinib for Lung and Thyroid Cancers With RET Gene Mutations or Fusions." (2020), <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selpercatinib-lung-and-thyroid-cancers-ret-gene-mutations-or-fusions>.
5. U.S. Food and Drug Administration, "FDA Approves Selpercatinib for Locally Advanced or Metastatic RET Fusion-Positive Solid Tumors." (2022), <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selpercatinib-locally-advanced-or-metastatic-ret-fusion-positive-solid-tumors>.
6. U.S. Food and Drug Administration, "FDA Grants Accelerated Approval to Selpercatinib for Pediatric Patients Two Years and Older With RET-Altered Metastatic Thyroid Cancer or Solid Tumors." (2024), <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-selpercatinib-pediatric-patients-two-years-and-older-ret-altered>.
7. D. A. Morgenstern, L. Mascarenhas, M. Campbell, et al., "Oral Selpercatinib in Pediatric Patients (Pts) With Advanced RET-Altered Solid or Primary CNS Tumors: Preliminary Results From the Phase 1/2 LIBRETTO-121 Trial," *Journal of Clinical Oncology* 39, no. suppl 15 (2021): 10009, https://doi.org/10.1200/JCO.2021.39.15_suppl.10009.
8. A. Drilon, G. R. Oxnard, D. S. W. Tan, et al., "Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer," *New England Journal of Medicine* 383, no. 9 (2020): 813–824, <https://doi.org/10.1056/NEJMoa2005653>.
9. A. Drilon, V. Subbiah, O. Gautschi, et al., "Selpercatinib in Patients With RET Fusion-Positive Non-Small-Cell Lung Cancer: Updated Safety and Efficacy From the Registrational LIBRETTO-001 Phase I/II Trial," *Journal of Clinical Oncology* 41, no. 2 (2023): 385–394, <https://doi.org/10.1200/JCO.22.00393>.
10. D. Liu, J. Walin, A. Akil, et al., *Population Pharmacokinetics of Selpercatinib in Patients With an Advanced Solid Tumor, Including RET Fusion-Positive NSCLC, RET-Mutant MTC, and Other Tumors With Increased RET Activity* (PAGE, 2022), 30. Abstr 9968 Poster presented at PAGE Conference 2022, <https://www.page-meeting.org/?abstract=9968>.
11. Centers for Disease Control and Prevention, "1999-2004 Dual Energy X-ray Absorptiometry (DXA) Multiple Imputation Data Files." <https://wwwn.cdc.gov/nchs/nhanes/dxa/dxafaq.aspx>. NHANES.

12. F. Salem, T. N. Johnson, K. Abduljalil, G. T. Tucker, and A. Rostami-Hodjegan, "A Re-Evaluation and Validation of Ontogeny Functions for Cytochrome P450 1A2 and 3A4 Based on In Vivo Data," *Clinical Pharmacokinetics* 53, no. 7 (2014): 625–636, <https://doi.org/10.1007/s40262-014-0140-7>.

13. R. D. Mosteller, "Simplified Calculation of Body-Surface Area," *New England Journal of Medicine* 317, no. 17 (1987): 1098, <https://doi.org/10.1056/NEJM198710223171717>.

14. S. L. Beal, L. B. Sheiner, A. J. Boeckmann, et al., "NONMEM 7.5 User's Guides." (1989-2020).

15. L. Lindbom, P. Pihlgren, and E. N. Jonsson, "PsN-Toolkit—A Collection of Computer Intensive Statistical Methods for Non-Linear Mixed Effect Modeling Using NONMEM," *Computers in Biology and Medicine* 79, no. 3 (2005): 241–257, <https://doi.org/10.1016/j.cmpb.2005.04.005>.

16. R Core Team, "R: A Language and Environment for Statistical Computing." (2019), R Foundation for Statistical Computing, Vienna, Austria, <https://www.R-project.org/>.

17. M. Bergstrand, A. C. Hooker, J. E. Wallin, and M. O. Karlsson, "Prediction-Corrected Visual Predictive Checks for Diagnosing Non-linear Mixed-Effects Models," *AAPS Journal* 13, no. 2 (2011): 143–151, <https://doi.org/10.1208/s12248-011-9255-z>.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.