Clinical and Translational Science

ARTICLE OPEN ACCESS

Elexacaftor/Tezacaftor/Ivacaftor Population Pharmacokinetics in Pediatric Patients With Cystic Fibrosis

Ngoc Hoa Truong[1,2] | Sihem Benaboud[1,2] | Naïm Bouazza[1,3,4] | Mahassen Barboura[5] | Emmanuelle Bardin[5] | Michel Miralles[2] | Gabrielle Lui[1,2] | Léo Froelicher-Bournaud[1,2] | Steeve Rouillon[2] | Tiphaine Bihouee[6] | Stéphanie Bui[7] | Philippe Reix[8] | Marie-Laure Dalphin[9] | Muriel Laurans[10] | Jeanne Languepin[11] | Harriet Corvol[12] | Françoise Troussier[13] | Laurence Weiss[14] | Rames Cinthia[15] | Aurélie Tatopoulos[16] | Eric Deneuville[17] | Raphael Chiron[18] | Nathalie Stremler[19] | Cathy Llerena[20] | Sophie Ramel[21] | Caroline Perisson[22] | Véronique Houdoin[23] | Marie Mittaine[24] | Jean-Marc Treluyer[1,2,3,4] | Isabelle Sermet-Gaudelus[5,25,26] | Frantz Foissac[1,3,4] | MODUL-CF study group

[1]Pharmacologie et Évaluations des Thérapeutiques Chez L'Enfant et la Femme Enceinte, Université Paris Cité, Inserm, Paris, France | [2]Service de Pharmacologie Clinique, Hôpital Cochin, AP-HP, Université Paris Cité, Paris, France | [3]Unité de Recherche Clinique Necker Cochin, AP-HP, Paris, France | [4]CIC-1419 Inserm, Cochin-Necker, Marseille, France | [5]Hôpital Necker Enfants Malades, Centre de Référence Maladies Rares Mucoviscidose et Maladies apparentées, Paris, France | [6]Chronic Childhood Diseases Unit, Pediatric Department, Nantes University Hospital, Nantes, France | [7]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires de Bordeaux, Bordeaux, France | [8]Centre de Ressources et de Compétences Pour la Mucoviscidose, Site Pédiatrique, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Lyon, France | [9]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires de Besançon, Besançon, France | [10]Centre de Ressources et de Compétences de la Mucoviscidose, Centre Hospitalier Universitaire de Caen Normandie, Caen, France | [11]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires de Limoges, Limoges, France | [12]Inserm U938, Centre de Recherche Saint-Antoine (CRSA), Assistance Publique—Hôpitaux de Paris (AP-HP), Hôpital Trousseau, Service de Pneumologie Pédiatrique, Sorbonne Université, Paris, France | [13]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires D'angers, Angers, France | [14]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires de Strasbourg, Strasbourg, France | [15]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires de Amiens, Amiens, France | [16]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires de Nancy, Nancy, France | [17]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires de Rennes, Rennes, France | [18]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires de Montpellier, Montpellier, France | [19]Paediatric Cystic Fibrosis Resources and Competences Centre, CHU de Marseille, Hôpital de la Timone, France | [20]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires de Grenoble, Grenoble, France | [21]Centre de Ressources et de Compétences de la Mucoviscidose, Fondation Ildys, Roscoff, France | [22]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires de Félic-Guyon, Réunion, France | [23]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Robert-Debré, Paris, France | [24]Centre de Ressources et de Compétences de la Mucoviscidose, Hôpitaux Universitaires de Toulouse, Toulouse, France | [25]European Reference Network, Lung, Frankfurt, Germany | [26]Institut Necker Enfants Malades, INSERM U1151, Paris, France

Correspondence: Ngoc Hoa Truong (ngochoa.truong@aphp.fr)

Received: 7 March 2025 | **Revised:** 16 April 2025 | **Accepted:** 22 April 2025

Funding: The authors received no specific funding for this work.

Keywords: CFTR modulators | cystic fibrosis | pediatrics | pharmacokinetics | therapeutic drug monitoring

ABSTRACT

Elexacaftor/tezacaftor/ivacaftor (ETI) significantly improves treatment outcomes for people with cystic fibrosis (pwCF) with at least one F508del allele. In 2023, the Food and Drug Administration approved ETI for children with CF aged 2–5 years. However, real-world pharmacokinetic-pharmacodynamic data for ETI in pediatric and adult populations are still limited. This study aimed to characterize the population PK of ETI in children with CF (chCF) and evaluate current dosing recommendations. Population PK modeling was conducted using Monolix software on 150 ETI concentrations obtained from therapeutic drug

*See the Acknowledgments section for the MODUL-CF study group.

(TDM) monitoring in 96 children with CF aged 2–18 years, as part of the MODUL-CF study. Area under the curve was derived from individual Bayesian pharmacokinetic estimates. A one-compartment model with a lag time, first-order absorption, and elimination best described the PK of elexacaftor/ivacaftor, while the PK of tezacaftor followed a one-compartment model with first-order absorption and elimination. A large between-subject variability was observed. The effect of body weight was significant on apparent clearance and volume of distribution parameters using allometric scaling. Children weighing 30–40 kg who received the adult-recommended dose showed higher drug exposure compared to adults with cystic fibrosis. This is the first study to describe the population pharmacokinetics of ETI in chCF aged 2–18 years, revealing high between-subject variability for all three drugs. In this context, TDM is likely essential for managing ETI exposure levels and guiding dosing adjustments. The appropriateness of current dosing recommendations for children under 12 years old weighing 30–40 kg remains to be clarified.

Summary

- What is the current knowledge on the topic?
  - ETI significantly improves the care and clinical outcomes of people with cystic fibrosis (pwCF) who have at least one F508del allele. However, real-world pharmacokinetic data of ETI in pediatric populations remain scarce, raising concerns about the appropriateness of current dosing recommendations.
- What question did this study address?
  - This study aimed to characterize the population pharmacokinetics of ETI in children with CF aged 2–18 years and assess whether current dosing recommendations achieve expected adult drug exposure.
- What does this study add to our knowledge?
  - The analysis revealed a high between-subject variability in ETI pharmacokinetics and a significant effect of body weight on apparent drug clearance and distribution. Children with CF weighing 30–40 kg who received the adult-recommended dose exhibited higher drug exposure than adults with CF.
- How might this change clinical pharmacology or translational science?
  - The findings highlight the importance of therapeutic drug monitoring in managing ETI exposure in children with CF. By considering interindividual variability and the key factors influencing it, along with exploring potential dosing strategies, this study contributes to optimizing ETI therapy for children with CF.

1 | Introduction

Cystic fibrosis (CF), an autosomal recessive inherited disease initially identified in the Caucasian population, affects over 100,000 people worldwide [1–4]. The discovery of the *CFTR* gene (Cystic Fibrosis Transmembrane Conductance Regulator) in 1989 revolutionized the understanding of CF pathophysiology [5]. The *CFTR* gene encodes a protein that regulates chloride and bicarbonate transport in secretory epithelia, crucial for hydration and antimicrobial defense in organs like the lungs and pancreas. Mutations in the *CFTR* gene impair these processes, leading to dehydration of the airway surface liquid and the pulmonary symptoms characteristic of CF [6, 7]. The most common mutation, found in about 90% of people with CF (pwCF) on at least one allele, is the deletion of phenylalanine at position 508 (F508del), which causes CFTR protein misfolding and dysfunction [8]. Since the discovery of the most common mutation, more than 2000 additional *CFTR* mutations have been identified [9].

CFTR modulators are small-molecule drugs that partially restore the function of defective CFTR proteins. There are 2 main types of CFTR modulators: potentiators (e.g., ivacaftor) and correctors (e.g., elexacaftor and tezacaftor). CFTR potentiators enhance the function of existing CFTR proteins at the cell surface, while CFTR correctors help defective CFTR proteins fold correctly and reach the cell surface in greater numbers [10]. Ivacaftor was the first modulator to be approved in 2012 and was first introduced as a monotherapy for pwCF with the G551D mutation.

The triple-combination regimen of elexacaftor/tezacaftor/ivacaftor (ETI) was initially approved by the European Medicines Agency (EMA) in August 2020 for the treatment of children with CF (chCF) aged 12 and older with normal liver function. Since then, the EMA has granted two additional labeling extensions for ETI: the first in January 2022, extending its use to chCF aged 6–11, and the second in November 2023, approving it for children aged 2–5. These approvals apply to chCF who have at least one copy of the F508del mutation or other mutations that have demonstrated responsiveness to ETI in in vitro studies [11].

CFTR modulators' overall efficacy has been proven in numerous clinical trials involving both children and adults [12–16]. However, a wide variability in response to the treatment has also been observed. This variability may be partly attributed to interindividual variability in pharmacokinetics. Furthermore, the anatomical and physiological differences between pediatric and adult populations can significantly affect the drug's absorption, distribution, and elimination processes. For instance, in children, drug metabolism varies with age and weight, and between-subject variability in pharmacokinetic parameters could be greater in children than in adults due to developmental changes in hepatic enzymes [17]. ETI molecules are extensively metabolized, predominantly in the liver by cytochrome P450 3A, including both CYP3A4 and CYP3A5 [18–20].

To date, chCF has received the recommended dose of ETI based on their body weight and age [11]. However, limited research has investigated the pharmacokinetics (PK) and the pharmacokinetic-pharmacodynamic (PKPD) relationships of ETI in chCF in real-world settings [12, 13, 21]. Recently, Bouazza et al. showed a significant association between ivacaftor exposure, in combination with lumacaftor (a CFTR corrector), and changes from baseline in forced expiratory volume in one

second (FEV_1) after 48 weeks of treatment [22]. However, the dose–response and dose-toxicity relationships of ETI in the pediatric population remain poorly understood, highlighting the need for PK studies to optimize treatment efficacy and safety.

The objectives of this study were to describe the population PK of elexacaftor, tezacaftor, and ivacaftor in chCF, to identify factors explaining interindividual variability, and to evaluate current dosing recommendations.

2 | Methods

2.1 | Patients and Setting

This PK analysis was an ancillary study of the MODUL-CF French prospective multicenter cohort study evaluating the response to CFTR modulators in chCF. This study was approved by the ethics committee (Comité de Protection des Personnes, Nord Ouest IV, no. EUDRACT: 2018-002624-16) and registered in the clinicaltrials.gov database under reference NCT03894657. This pharmacokinetic sub-study included data from 20 pediatric university hospital centers between March 2022 and March 2024. The main inclusion criteria were chCF aged 2–18 with at least one F508del mutation, who were receiving and adhering to ETI treatment as per marketing authorization and undergoing therapeutic drug monitoring.

2.2 | Data Collection and Sampling

Blood samples for the pharmacokinetic study were collected via venipuncture during scheduled follow-up clinical visits in the MODUL-CF study or at the specific request of clinicians. The blood samples were collected as follows: a trough concentration was measured just before ETI intake and/or a peak concentration was measured around 4 h after intake. Overall, the dose received, the type of ETI formulation (granules or tablet), and the time elapsed between administration and sampling times were carefully recorded. Clinical data was retrospectively recorded from electronic medical records, including weight, height, sex, and age of the chCF.

2.3 | Analytical Method

Ivacaftor (IVA), tezacaftor(TEZ), and elexacaftor(ELX) were assayed using a liquid chromatography coupled with a tandem mass spectrometry method (LC–MS/MS) (Waters, Milford, USA) as previously described in detail [23]. The technique was validated according to EMA guidelines in the range of 0.075–20 mg/L for tezacaftor and elexacaftor, and of 0.0525–14 mg/L for ivacaftor.

2.4 | Pharmacokinetic Analysis

Data were analyzed using the nonlinear mixed effect modeling software program Monolix version 2023R1 (https://lixoft.com). Parameters were estimated by the Markov Chain Monte Carlo-Stochastic Approximation Expectation Maximization algorithm (MCMC-SAEM). Different structural models were evaluated to model elexacaftor, ivacaftor, and tezacaftor concentrations: one or two compartments, using first-order absorption with or without delay in absorption, and first-order elimination or Michaelis–Menten's elimination. The between-subject variabilities (BSV) were ascribed to an exponential model. To characterize the residual variability, three error models (i.e., proportional, additive, and combined error models) were investigated. Data below the Limit of Quantification (LOQ) were handled as left-censored data by Monolix.

The likelihood ratio test, including the log-likelihood, the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), was used to assess model fitting and to compare the different models.

The main covariates tested were age (AGE), bodyweight (WT), body mass index (BMI), body surface area (BSA), sex, as well as the type of ETI formulation (granules or tablet, GAL).

Binary covariates (CAT) were tested according to the following equation,

$$\mathrm{CL} = \theta_{\mathrm{CL}} \bullet \left(\beta_{\mathrm{CAT}}^{\mathrm{CL}}\right)^{1}$$

where $\beta_{\mathrm{CAT}}^{\mathrm{CL}}$ is the estimated influential factor for the binary covariate, CAT = 0 stands for the reference θ_{CL} value and CAT = 1 for the CL value in the presence of the covariate.

Continuous covariates were tested according to the following equation, using clearance (CL) for example,

$$\mathrm{CL} = \theta_{\mathrm{CL}} \bullet \left(\frac{\mathrm{COV}}{\mathrm{median(COV)}}\right)^{\beta_{\mathrm{COV}}^{\mathrm{CL}}}$$

where θ_{CL} is the typical value of clearance for a patient with the median covariate value and $\beta_{\mathrm{COV}}^{\mathrm{CL}}$ is the estimated influential factor for the continuous covariate.

For WT, according to allometric scaling theory, the power exponent is typically set to 0.75 for clearance and 1 for volume of distribution parameters. Additionally, age-related functions were evaluated to account for maturation effects on CL/F and bioavailability parameters, as previously described [24–26].

The quality of each model was evaluated by visual inspection of the observed-predicted (population and individual) concentration scatter plots. Diagnostic graphics and other statistics were obtained using the R software. From the final model, simulations were performed to compute the prediction-corrected visual predictive checks (pcVPC) and the normalized prediction distribution error (NPDE) metrics. Individual pharmacokinetic parameter estimates were obtained through Bayesian estimation from the final model.

For each chCF, we then derived the following pharmacokinetic parameters: maximum concentration (C_{max}), trough concentration (C_{trough}) at 24 h for elexacaftor and tezacaftor and at 12 h for

ivacaftor, and areas under the curves (AUC_{0-24h} for elexacaftor and tezacaftor; AUC_{0-12h} for ivacaftor).

2.5 | Simulation of the Current Dosing Recommendations

Using the final ETI pharmacokinetic models, we conducted simulations to evaluate the current pediatric dosing recommendations. For children weighing less than 14 kg, the prescribed doses were elexacaftor 80 mg once daily, tezacaftor 40 mg once daily, and ivacaftor 60 mg each morning and 59.5 mg each evening. Children weighing between 14 and 30 kg received elexacaftor 100 mg once daily, tezacaftor 50 mg once daily, and ivacaftor 75 mg every 12 h. For children over 30 kg or older than 12 years, the doses were elexacaftor 200 mg once daily, tezacaftor 100 mg once daily, and ivacaftor 150 mg every 12 h. We developed a virtual pediatric population of 2000 patients with body weights ranging from 10 to 60 kg and performed PK simulations using the ETI final models, applying the corresponding ETI-recommended doses for each weight range. From the obtained pharmacokinetic profiles, we derived the AUC parameter for elexacaftor, tezacaftor, and ivacaftor. We compared the ETI AUC values to those reported by Zemanick et al. [13]. Based on the simulation outcomes, we evaluated the potential for dose refinements within the constraints of existing dosage forms, with the goal of optimizing exposure in the pediatric population while maintaining AUC_{0-24h} values within the adult reference range (5th to 95th percentiles). All simulations and graphical outputs were generated using the R software.

3 | Results

3.1 | Population Characteristics and Available Data

Pharmacokinetic evaluations were conducted on 96 children (66.7% males), with baseline characteristics detailed in Table 1. For the pharmacokinetic analysis, 150 concentration measurements were collected for each compound—elexacaftor, ivacaftor, and tezacaftor. The median number of samples per chCF per compound was 1, ranging from 1 to 5. Across all three compounds, only one sample fell below LOQ, which was an ivacaftor concentration measurement from a 3-year-old patient.

3.2 | Pharmacokinetic Analysis

A one-compartment model with first-order absorption and elimination optimally described the pharmacokinetics of tezacaftor, while the pharmacokinetics of elexacaftor and ivacaftor were best fitted by a one-compartment model incorporating absorption lag time, first-order absorption, and elimination. Given the limited number of plasma samples available during the absorption phase in this study, the absorption parameters (i.e., lag time [T_{lag}] and/or absorption constant [K_a]) were set to values reported in the literature for the three molecules [27]. For all drugs, the available data allowed estimating BSVs for the apparent clearance parameter. A proportional residual error model was retained for elexacaftor/tezacaftor and a combined residual error model for ivacaftor. Among the various size descriptors, including BMI, BSA, and bodyweight, the latter showed the most significant effect. Specifically, bodyweight, applied through allometric scaling, significantly impacted both the clearance and volume of distribution of these compounds. According to the allometric rule, the power exponents for bodyweight effect were fixed to 0.75 and 1 for the apparent clearance and the apparent volume of distribution parameters. The inclusion of bodyweight through allometric scaling significantly decreased the BIC with $\Delta BIC_{elexacaftor} = 64.5$, $\Delta BIC_{tezacaftor} = 84.2$ and $\Delta BIC_{ivacaftor} = 35.2$. The BSV for apparent clearance was reduced from 0.48 to 0.31 for elexacaftor, from 0.39 to 0.26 for tezacaftor, and from 0.48 to 0.37 for ivacaftor. None of the other covariates including AGE, SEX, and GAL were related to PK parameters. Table 2 summarizes the final population pharmacokinetic estimates for the three compounds.

The pcVPC plots show that the average predicted concentrations align well with the observed concentration time-profiles and that the variability is within the expected range for elexacaftor, ivacaftor, and tezacaftor (Figure 1). Figure S1 presents a comparison of observed versus population-predicted concentrations (DV versus PRED) and between observed versus individual-prediction concentrations (DV vs. IPRED). The NPDE analysis showed normally distributed errors, with no major trends in

TABLE 1 | Descriptive statistics at baseline for subjects included in the PK analysis.

Demographics and clinical characteristics			
Number of children			96
Number of samples per molecule			150
Age group	< 6 years $N = 47$	6 ≥ years < 12 years $N = 19$	≥ 12 years $N = 30$
Male	34	13	17
Age (years), median [IQR]	4.0 [3.2–5.0]	8.8 [7.0–10.4]	15.8 [14.6–16.6]
Weight (kg), median [IQR]	16.0 [14.0–17.5]	25.0 [21.6–31.2]	51.1 [44.5–57.5]
Height (cm), median [IQR]	102.0 [94.5–107.8]	128.0 [117.2–138.0]	161.3 [156.9–170.9]
BMI (kg/m^2), median [IQR]	15.6 [14.6–16.3]	15.3 [14.9–16.8]	18.9 [17.4–21.5]
BSA (m^2), median [IQR]	0.7 [0.61–0.73]	0.94 [0.86–1.06]	1.52 [1.40–1.64]

TABLE 2 | Parameters of the final ETI population pharmacokinetic models.

	Estimate (% RSE)		
	Elexacaftor	**Tezacaftor**	**Ivacaftor**
Fixed effects			
T_{lag} (h)	2.17 (fix)	—	0.70 (fix)
K_a (h^{-1})	0.59 (fix)	0.894 (fix)	0.42 (fix)
CL/*F* (L/h/70 kg)	1.57 (3.9)	1.32 (3.8)	13.4 (4.8)
V/*F* (L/70 kg)	56.1 (9.9)	29.3 (6.8)	183 (12.6)
Between-subject variability			
ω_{CL}	0.31 (11.1)	0.26 (14.8)	0.37 (12.4)
Residual error			
σ additive (mg/L)	—	—	0.131 (43.0)
σ proportional	0.247 (9.2)	0.302 (8.5)	0.278 (12.5)

Abbreviations: σ, residual variability estimate; ω, interindividual variability estimate expressed as standard deviation; CL/*F*, apparent elimination clearance; K_a, absorption rate constant; RSE, relative standard error (standard error of estimate/estimate*100); T_{lag}, lag time; *V*/*F*, apparent volume of distribution.

NPDE versus time or NPDE versus predictions (Figure S2). The NPDE of the three final models is deemed valid, as they successfully pass both the symmetry and normality tests. Table 3 summarizes ETI $AUC_{0\text{-}\tau}$, C_{trough}, and C_{max} values obtained in this study alongside previously reported values for adults. Table S1 provides a detailed breakdown of pharmacokinetic parameters according to dosing recommendations, categorized by the weight and age groups of the children.

3.3 | Simulation of the Current Dosing Recommendations

Figure 2 presents boxplots of ETI exposures ($AUC_{0\text{-}\tau}$h) based on 2000 simulations of the final PK models, following current dosing recommendations by weight bands (ranging from 10 to 60 kg). Figure S3 shows the proportion of chCF across weight bands who achieved an AUC within the 90% confidence interval of adult-reported values, below the 5th percentile, or above the 95th percentile of adult-reported AUC values. Simulation results suggested a potential risk of elevated drug exposure in chCF weighing between 30 and 40 kg. Specifically, more than 40% of chCF in the 30–35 kg weight range had simulated AUC values exceeding the 95th percentile of adult-reported AUC values, indicating a higher risk of elevated exposure: 42.6% for elexacaftor, 61.4% for tezacaftor, and 40.1% for ivacaftor. This risk remains high in the 35–40 kg weight range, with 34.2% for elexacaftor, 44.4% for tezacaftor, and 34.1% for ivacaftor.

To explore potential strategies for optimizing ETI exposure, we performed exploratory simulations, starting with a scenario where children with CF weighing 30–40 kg were administered half of the recommended adult dose, instead of the full adult dose currently recommended. The simulated AUC_{0-24h} for ETI indicated that, while only 2% of chCF would be at risk of elevated exposure, this dosing regimen could also pose a significant risk of underexposure, with up to 35% of chCF having AUC values below the 5th percentile of adult AUC values (see Figures S4A and S5A). A second dosing regimen was therefore explored to optimize the proportion of children weighing 30–40 kg falling within the 5th to 95th percentiles of adult AUC values while remaining consistent with available dosage forms. The ETI daily dose consists of 150 mg of elexacaftor, 75 mg of tezacaftor, and 231.5 mg of ivacaftor, administered as 112.5 mg in the morning and 119 mg in the evening. The simulation results indicate that this dosing adjustment could reduce the proportion of AUC_{0-24h} values exceeding the adult 95th percentile threshold (see Figures S4B and S5B) compared to those observed with the current dosing recommendation in this population. For chCF weighing 30–35 kg, the proportions decrease to 14.2% for elexacaftor, 21.3% for tezacaftor, and 20% for ivacaftor. In the 35–40 kg group, the proportions drop to 8.9% for elexacaftor, 12.9% for tezacaftor, and 7.7% for ivacaftor.

4 | Discussion

This study examines the population pharmacokinetics of ETI in chCF aged 2–18 years, providing the first comprehensive real-world PK analysis of this combination therapy in this population. Elexacaftor and ivacaftor concentrations were satisfactorily described by a 1-compartment model with an absorption lag time. The PK of tezacaftor was best described by a one-compartment model with first-order absorption and elimination. We could not fully characterize the absorption phase, as the plasma samples in our study were collected primarily for therapeutic drug monitoring at peak and/or trough concentrations. As a result, the parameters for the absorption phase were set to previously reported values for all three molecules [27]. ETI apparent clearance and volume of distribution parameters were shown to significantly increase with body weight. Body weight was incorporated into the ETI models, applying an exponent of 1 for V/F and 3/4 for CL/F in line with allometric scaling theory. This enabled us to extrapolate pharmacokinetic parameters from children to adult values, facilitating the standardization of results and effectively accounting for weight variability within our population. This study showed that the main PK parameters of ETI, when standardized to a 70 kg individual, are close to those observed in adult pwCF [11, 13, 21]. The estimated apparent clearances of ELX, TEZ, and IVA for a 70 kg patient at steady state were 1.57, 1.32, and 13.4 L/h, respectively. These values are consistent with those previously reported, specifically a clearance of 1.4 L/h for ELX in a tritherapy regimen [28] and clearance values of 1.27 L/h for TEZ and 17 L/h for IVA in the IVA/TEZ combination therapy [29]. Following the administration of the fixed-dose combination of ETI, the half-lives ($t_{1/2}$) of ELX, TEZ, and IVA were approximately 24.7 [28], 15.4, and 9.5 h, respectively. These values are somewhat close to the effective half-lives previously reported, which were 29.8 h for ELX, 17.4 h for TEZ, and 15.0 h for IVA [29].

Interestingly, we observed substantial between-subject variability in the clearance of all three drugs studied. This high variability in pharmacokinetic parameters can be partly attributed to

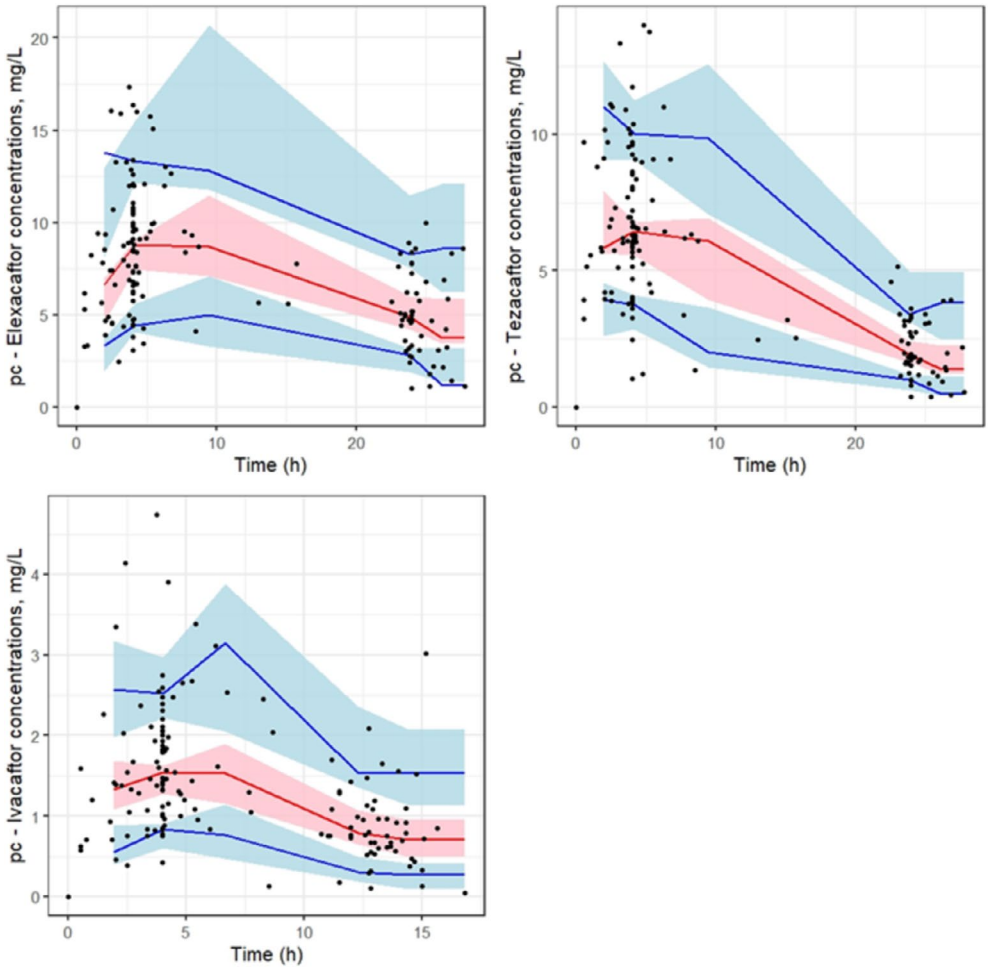

FIGURE 1 | Prediction-corrected visual predictive check (pcVPC) plots for ETI. The lines show the 10th, 50th, and 90th percentiles of observed data. The areas represent the 95% confidence interval around the simulated percentiles.

TABLE 3 | Individual estimated PK parameters.

ETI PK parameters	This study population, $n = 96$ median [IQR]	Reference adult PK parameters mean (SD) Choong et al.
ELX C_{max} (mg/L)	9.29 [7.95–11.1]	8.77 (2.16)
ELX C_{trough} (mg/L)	5.05 [3.96–6.61]	5.49 (2.65)
ELX AUC_{0-24} (mg*h/L)	172.9 [142.5–208.2]	167.0 (50.5)
TEZ C_{max} (mg/L)	6.83 [5.89–8.03]	6.69 (1.39)
TEZ C_{trough} (mg/L)	2.00 [1.55–2.71]	2.05 (0.81)
TEZ AUC_{0-24} (mg*h/L)	100.8 [87.0–119.8]	92.4 (23.8)
IVA C_{max} (mg/L)	1.48 [1.30–1.82]	1.27 (0.35)
IVA C_{trough} (mg/L)	0.84 [0.68–1.14]	0.75 (0.33)
IVA AUC_{0-12} (mg*h/L)	14.1 [12.2–18.0]	12.1 (4.17)

Abbreviations: AUC, area under the curve; C_{max}, maximal concentration; C_{trough}, trough concentration; ELX, elexacaftor; IVA, ivacaftor; TEZ, tezacaftor.

differences in body size. When applying allometric scaling, the between-subject variability in apparent clearance decreased for the three drugs. Among the size descriptors, body weight was identified as the covariate with the greatest impact on clearance and volume of distribution. No other significant relationships were identified between age, sex, drug formulation, and pharmacokinetic parameters. To further explore the impact of age, a maturation model was applied to both CL/F and bioavailability parameters. However, these models did not enhance the fit for the three drugs. This outcome is likely because the maturation

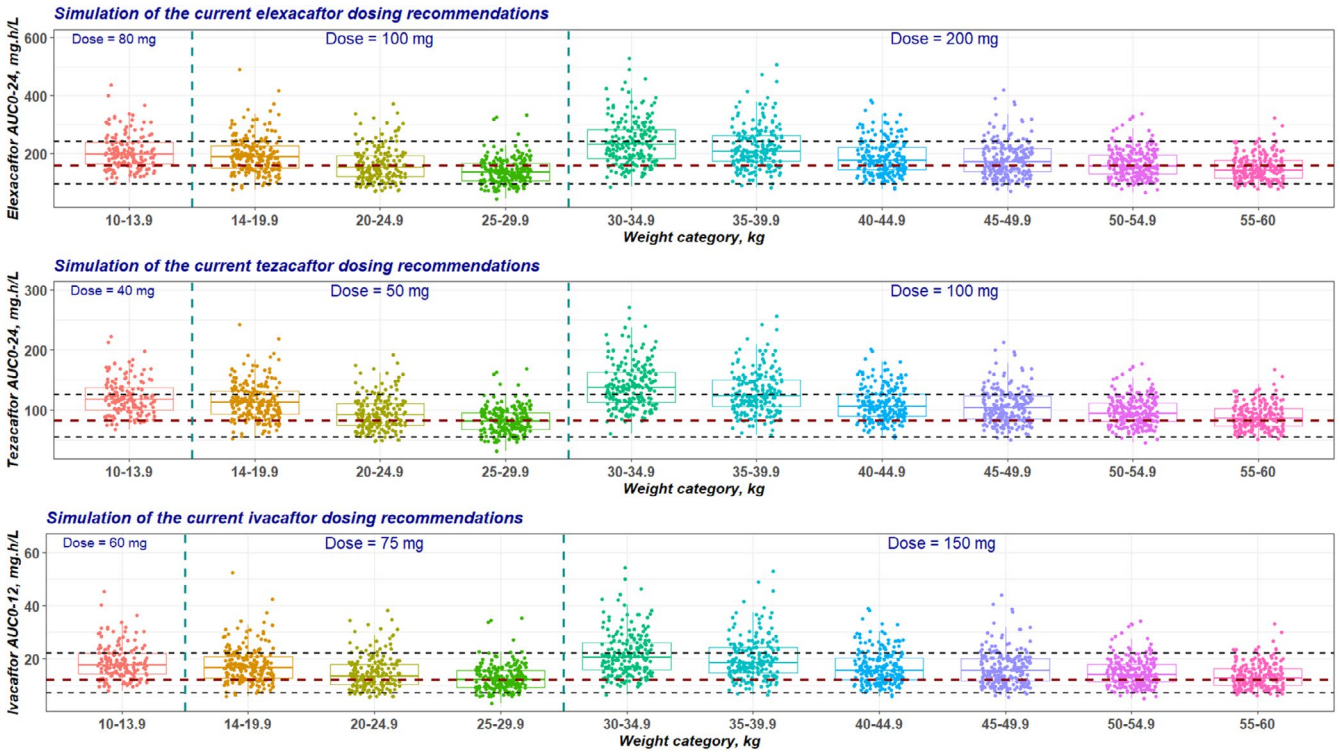

FIGURE 2 | Boxplots of the ETI exposures ($AUC_{0\text{-}\tau}$) obtained from 2000 simulations of the final PK models using the current dosing recommendations. AUC boxplots were presented as a function of different weight bands. For each graph, the dashed horizontal line represent the median of the adult AUC values, and the gray horizontal lines indicates the 5th (bottom line) and 95th percentiles (top line) of the adult AUC values.

of cytochromes CYP3A4/5, the primary enzymes responsible for ETI metabolism, reaches 80% of adult levels by the age of two [17].

Current pediatric dosing recommendations are primarily based on a child's body weight and age, with the goal of achieving drug exposure levels similar to those in adults receiving the standard dose. We used in this study the same adult exposure targets to evaluate the current dosing recommendation in terms of ETI drug exposure [13].

As mentioned earlier, our study did not identify any additional impact of age on the pharmacokinetics of ETI. Thus, simulations of the current pediatric dosing recommendations were conducted using the final ETI models in a patient population weighing between 10 and 60 kg. These simulations aimed to obtain the distribution of $AUC_{0\text{-}\tau}$ across various weight bands and to compare them with the 90% confidence interval reported for the adult drug dosage. These simulations indicate that the recommended ETI dosing appears to be appropriate for children weighing 20–25 kg and those weighing more than 40 kg. For chCF weighing less than 20 kg, our simulations indicated a risk of elevated exposure, particularly for chCF weighing less than 14 kg. However, there is currently no suitable dosage form available to adjust the recommended doses for chCF under 14 kg. For chCF weighing between 25 and 30 kg, our comparison of the ETI AUC values with those reported by Zemanick et al. showed that up to 15% of these children could be at risk of underdosing, as their simulated AUC values fell below the 5th percentile of the adult AUC values. Therapeutic drug monitoring is likely essential for managing ETI exposure levels and guiding dosing adjustments. Regarding children weighing 30 kg or more, the current dosing recommendation is to shift to adult dosing. However, our simulations indicate that administering the adult dosage to children in the 30–40 kg weight range may substantially increase the risk of higher exposure compared to heavier weight groups, i.e., up to 60% of chCF above the 95th percentile of the adult AUC values. These observations align with those of the summary of product characteristics published by the EMA, which reported elevated AUC levels in chCF weighing more than 30 kg who received the standard adult dose [11].

Currently, the ETI combination therapy is available in just four dosage forms: two tablet formulations (ETI: 50/25/37.5 and 100/50/75 mg) and two packet formulations (ETI: 50/25/37.5 and 80/40/60 mg), the latter intended for pediatric use in chCF under 6 years of age. Through simulation, we explored the ETI AUC distribution achievable with a reduced dosing regimen for children with CF weighing 30–40 kg, in accordance with available dosage forms. In this scenario, children in this weight range would receive a morning dose of three tablets of ETI 50/25/37.5 mg and an evening dose of two packets of ivacaftor 59.5 mg. This dosing approach could help achieve optimal exposure by maintaining $AUC_{0\text{–}24h}$ within the adult reference range (5th to 95th percentiles). However, simulation results also indicate a residual risk, with 21% of chCF in the 30–35 kg group and 12.9% in the 35–40 kg group still exceeding this threshold. These findings underscore the need for further clinical evaluations to specifically assess the appropriateness of current dosing recommendations for children with CF weighing 30–40 kg.

This observational pharmacokinetic study has several limitations. First, it is based on a sparse sampling design, with limited PK samples collected per patient. Second, as previously noted, we were unable to accurately characterize the absorption phase due to insufficient sampling within the first 2 h post-dose. Third, we lacked dietary fat intake information for each administration, precluding evaluation of food's impact on drug bioavailability. The summary of product characteristics specifies that food significantly enhances the absorption and bioavailability of elexacaftor and ivacaftor, but not tezacaftor [11]. When taken with a moderate-fat meal, $AUC_{0-\infty}$ increases 1.9- to 2.5-fold for ELX and 2.5- to 4-fold for ivacaftor compared to fasting conditions. Finally, our dataset did not include information on several other factors that might account for the high interindividual variability in CL/F observed in this study, such as CYP3A polymorphisms, ASAT/ALAT levels, and, to a lesser extent, serum creatinine levels. However, despite the absence of these covariates, none of our chCF had renal failure, liver disease, or coadministration of strong inducers or inhibitors.

An alternative dosing regimen was considered for children weighing 30–40 kg; however, these simulations were exploratory in nature and should not be interpreted as evidence supporting any modification to current dosing recommendations.

Currently, the pharmacokinetic-pharmacodynamic relationships between ETI drug exposure levels and efficacy/tolerance remain undefined. As a result, the exposure targets utilized in this study were based on Zemanick's adult exposure data, which were already applied to derive the current pediatric dosing recommendations [13]. Further investigations are required to better characterize the PKPD of ETI in the pediatric population.

This study primarily aims to establish the first population pharmacokinetics models for ETI using real-world data in chCF aged 2–18 years and to assess the current pediatric dosing recommendations. Children weighing 30–40 kg who received the adult-recommended dose showed higher drug exposure compared to adults with CF. Our findings support the use of therapeutic drug monitoring for ETI in this population to better personalize dosing and identify or exclude cases of higher drug exposure or underexposure. Future research should further investigate the impact of genetic, clinical, physiological, and environmental factors on ETI pharmacokinetics, as well as investigate the relationship between ETI drug exposure, efficacy, and toxicity.

Author Contributions

N.H.T., S.B., and F.F. wrote the manuscript. N.H.T., S.B., F.F., N.B., J.M.T., and I.S.G. designed the research. N.H.T., S.B., M.B., E.B., T.B., S.B., P.R., M.L.D., M.L., J.L., H.C., F.T., L.W., R.C., A.T., E.D., R.C., N.S., C.L., S.M., C.P., V.H., M.M., and I.S.G. performed the research. N.H.T., S.B., F.F., N.B., L.F.B., S.R., M.M., and G.L. analyzed the data.

Acknowledgments

This ancillary study of MODUL-CF received no specific funding. The authors thank the patients and the parents of pediatric patients who participated in this study.

Modul-CF study group: Melissa Baravalle (Marseille); Mahassen Barboura (Paris-Necker); Audrey Barzic (Roscoff); Lilia Benhalla (Paris Necker); Khadidja Bennour (Paris-Necker); Katia Bessaci (Reims); Antoine Bessou (Paris-Vaincre la Mucoviscidose); Thiphaine Bihouée (Nantes); Anne-Sophie Bonnel (Versailles); Nesrine Bouleghem (Paris Necker); Stéphanie Bui (Bordeaux); Frédérique Chedevergne (Paris-Necker); Harriet Corvol (Paris-Trousseau); Laure Cosson (Tours); Laure Couderc (Rouen); Marie Laure Dalphin (Besançon); Paola De Carli (Paris-Vaincre la Mucoviscidose); Eric Deneuville (Rennes); Pierre Foucaud (Paris-Vaincre la Mucoviscidose); Asma Gabsi (Versailles); Elsa Gachelin (La Réunion Saint-Denis); Fatiha Hassani (Paris-Necker); Véronique Houdouin (Paris-Robert Debré); Frédéric Huet (Dijon); Marie Jamin (Saint-Brieuc); Kadiatou Kaba (Paris-Vaincre la Mucoviscidose); Guillaume Labbé (Clermond-Ferrand); Jane Languepin (Limoges); Muriel Laurans (Caen); Cathy Léréna (Grenoble); Alexia Letierce (Paris Necker); Clotilde Livrozet (Vannes); Christophe Marguet (Rouen); Laurent Mély (Lyon); Rania Messaoudi (Paris-Necker); Marie Mittaine (Toulouse); Camille Ohlmann (Lyon); Caroline Périsson (La Réunion Saint-Pierre); Thomas Perrin (Lyon); Carole Piccini-Bailly (Nice); Cinthia Rames (Amiens); Philippe Reix (Lyon); Natascha Rémus (Créteil); Anna Ronayette (Paris-Vaincre la Mucoviscidose); Djouher Sahki (Paris Necker); Manuela Scalbert (Dunkerque); Isabelle Sermet (Paris-Necker); Floriane Socchi (Montpellier); Nathalie Stremler (Marseille); Aurélie Tatopoulos (Nancy); Guillaume Thouvenin (Paris-Trousseau); Tom Toin (Lyon); Françoise Troussier (Angers); Laurence Weiss (Strasbourg); Marie-Christine Werck-Galois (Lyon); Nathalie Wizla (Lille). Melissa Baravalle, Mahassen Barboura, Audrey Barzic, Lilia Benhalla, Khadidja Bennour, Katia Bessaci, Antoine Bessou, Thiphaine Bihouée, Anne-Sophie Bonnel, Nesrine Bouleghem, Stéphanie Bui, Frédérique Chedevergne, Harriet Corvol, Laure Cosson, Laure Couderc, Marie Laure Dalphin, Paola De Carli, Eric Deneuville, Pierre Foucaud, Asma Gabsi, Elsa Gachelin, Fatiha Hassani, Véronique Houdouin, Frédéric Huet, Marie Jamin, Kadiatou Kaba, Guillaume Labbé, Jane Languepin, Muriel Laurans, Cathy Léréna, Alexia Letierce, Clotilde Livrozet, Christophe Marguet, Laurent Mély, Rania Messaoudi, Marie Mittaine, Camille Ohlmann, Caroline Périsson, Thomas Perrin, Carole Piccini-Bailly, Cinthia Rames, Philippe Reix, Natascha Rémus, Anna Ronayette, Djouher Sahki, Manuela Scalbert, Isabelle Sermet, Floriane Socchi, Nathalie Stremler, Aurélie Tatopoulos, Guillaume Thouvenin, Tom Toin, Françoise Troussier, Laurence Weiss, Marie-Christine Werck-Galois, Nathalie Wizla.

Conflicts of Interest

Isabelle Sermet-Gaudelus declares fees for lectures and Educational support by Vertex Therapeutics. All other authors declare no conflicts of interest.

References

1. M. Shteinberg, I. J. Haq, D. Polineni, and J. C. Davies, "Cystic Fibrosis," *Lancet (London, England)* 397, no. 10290 (2021): 2195–2211.

2. S. D. Brown, R. White, and P. Tobin, "Keep Them Breathing: Cystic Fibrosis Pathophysiology, Diagnosis, and Treatment," *JAAPA* 30, no. 5 (2017): 23–27.

3. S. C. Bell, M. A. Mall, H. Gutierrez, et al., "The Lancet Respiratory Medicine Commission on the Future of Care of Cystic Fibrosis," *Lancet Respiratory Medicine* 8, no. 1 (2020): 65–124.

4. J. Guo, A. Garratt, and A. Hill, "Worldwide Rates of Diagnosis and Effective Treatment for Cystic Fibrosis," *Journal of Cystic Fibrosis* 21, no. 3 (2022): 456–462.

5. J. M. Rommens, M. C. Iannuzzi, B. Kerem, et al., "Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping," *Science* 245, no. 4922 (1989): 1059–1065.

6. L. S. Hanssens, J. Duchateau, and G. J. Casimir, "CFTR Protein: Not Just a Chloride Channel?," *Cells* 10, no. 11 (2021): 2844.

7. B. Lubamba, B. Dhooghe, S. Noel, and T. Leal, "Cystic Fibrosis: Insight Into CFTR Pathophysiology and Pharmacotherapy," *Clinical Biochemistry* 45, no. 15 (2012): 1132–1144.

8. Z. w. Cai, J. Liu, H. y. Li, and D. N. Sheppard, "Targeting F508del-CFTR to Develop Rational New Therapies for Cystic Fibrosis," *Acta Pharmacologica Sinica* 32, no. 6 (2011): 693–701.

9. M. Lopes-Pacheco, "CFTR Modulators: The Changing Face of Cystic Fibrosis in the Era of Precision Medicine," *Frontiers in Pharmacology* 10 (2020): 1662.

10. R. Jaques, A. Shakeel, and C. Hoyle, "Novel Therapeutic Approaches for the Management of Cystic Fibrosis," *Multidisciplinary Respiratory Medicine* 15, no. 1 (2020): 690.

11. "kaftrio-epar-product-information_en.pdf [Internet]," accessed August 5, 2024, https://www.ema.europa.eu/en/documents/product-information/kaftrio-epar-product-information_en.pdf.

12. J. L. Goralski, J. E. Hoppe, M. A. Mall, et al., "Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2–5 Years With Cystic Fibrosis and at Least One F508del Allele," *American Journal of Respiratory and Critical Care Medicine* 208, no. 1 (2023): 59–67.

13. E. T. Zemanick, J. L. Taylor-Cousar, J. Davies, et al., "A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age With Cystic Fibrosis and at Least One F508del Allele," *American Journal of Respiratory and Critical Care Medicine* 203, no. 12 (2021): 1522–1532.

14. M. A. Mall, R. Brugha, S. Gartner, et al., "Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age With Cystic Fibrosis Heterozygous for F508del and a Minimal Function Mutation: A Phase 3b, Randomized, Placebo-Controlled Study," *American Journal of Respiratory and Critical Care Medicine* 206, no. 11 (2022): 1361–1369.

15. S. Y. Graeber, C. Vitzthum, S. T. Pallenberg, et al., "Effects of Elexacaftor/Tezacaftor/Ivacaftor Therapy on CFTR Function in Patients With Cystic Fibrosis and One or Two F508del Alleles," *American Journal of Respiratory and Critical Care Medicine* 205, no. 5 (2022): 540–549.

16. C. Wainwright, S. A. McColley, P. McNally, et al., "Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged ≥6 Years With Cystic Fibrosis and at Least One F508del Allele: A Phase 3, Open-Label Clinical Trial," *American Journal of Respiratory and Critical Care Medicine* 208, no. 1 (2023): 68–78.

17. T. N. Johnson, A. Rostami-Hodjegan, and G. T. Tucker, "Prediction of the Clearance of Eleven Drugs and Associated Variability in Neonates, Infants and Children," *Clinical Pharmacokinetics* 45, no. 9 (2006): 931–956.

18. E. Hong, L. M. Almond, P. S. Chung, A. P. Rao, and P. M. Beringer, "Physiologically Based Pharmacokinetic Modeling to Guide Management of Drug Interactions Between Elexacaftor-Tezacaftor-Ivacaftor and Antibiotics for the Treatment of Nontuberculous Mycobacteria," *Antimicrobial Agents and Chemotherapy* 66, no. 11 (2022): e01104–e01122.

19. R. van der Meer, E. B. Wilms, and H. G. M. Heijerman, "CFTR Modulators: Does One Dose Fit All?," *Journal of Personalized Medicine* 11, no. 6 (2021): 458.

20. E. Hong, L. M. Almond, P. S. Chung, A. P. Rao, and P. M. Beringer, "Physiologically-Based Pharmacokinetic-Led Guidance for Patients With Cystic Fibrosis Taking Elexacaftor-Tezacaftor-Ivacaftor With Nirmatrelvir-Ritonavir for the Treatment of COVID-19," *Clinical Pharmacology and Therapeutics* 111, no. 6 (2022): 1324–1333.

21. E. Choong, A. Sauty, A. Koutsokera, S. Blanchon, P. André, and L. Decosterd, "Therapeutic Drug Monitoring of Ivacaftor, Lumacaftor, Tezacaftor, and Elexacaftor in Cystic Fibrosis: Where Are we Now?," *Pharmaceutics* 14, no. 8 (2022): 1674.

22. N. Bouazza, S. Urien, F. Foissac, et al., "Lumacaftor/Ivacaftor Population Pharmacokinetics in Pediatric Patients With Cystic Fibrosis: A First Step Toward Personalized Therapy," *Clinical Pharmacokinetics* 63, no. 3 (2024): 333–342.

23. Y. Zheng, S. Rouillon, M. Khemakhem, et al., "A Rapid LC-MS/MS Method for the Simultaneous Quantification of Ivacaftor, Lumacaftor, Elexacaftor, Tezacaftor, Hexyl-Methyl Ivacaftor and Ivacaftor Carboxylate in Human Plasma," *Journal of Pharmaceutical and Biomedical Analysis* 248 (2024): 116322.

24. B. J. Anderson and N. H. G. Holford, "Mechanistic Basis of Using Body Size and Maturation to Predict Clearance in Humans," *Drug Metabolism and Pharmacokinetics* 24, no. 1 (2009): 25–36.

25. B. J. Anderson and N. H. G. Holford, "Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics," *Annual Review of Pharmacology and Toxicology* 48 (2008): 303–332.

26. N. Holford, Y. A. Heo, and B. Anderson, "A Pharmacokinetic Standard for Babies and Adults," *Journal of Pharmaceutical Sciences* 102, no. 9 (2013): 2941–2952.

27. A. Tsai, S. P. Wu, E. Haseltine, et al., "Physiologically Based Pharmacokinetic Modeling of CFTR Modulation in People With Cystic Fibrosis Transitioning From Mono or Dual Regimens to Triple-Combination Elexacaftor/Tezacaftor/Ivacaftor," *Pulmonary Therapy* 6, no. 2 (2020): 275–286.

28. "210491Orig1s000ClinPharmR.pdf [Internet]," accessed August 28, 2024, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210491Orig1s000ClinPharmR.pdf.

29. "Multi-Discipline Review.pdf [Internet]," accessed August 28, 2024, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212273Orig1s000MultidisciplineR.pdf.

Supporting Information

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