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Real-world population pharmacokinetics of tezacaftor-ivacaftor in children with cystic fibrosis: the SYM-CF study

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January 16, 2025

Abstract

Aim: The clinical effectiveness of tezacaftor-ivacaftor in children with cystic fibrosis (cwCF) varies; some patients respond while others do not or have adverse effects. The pharmacokinetics (PK) of tezacaftor-ivacaftor are inadequately published, especially in children. Knowledge of the PK in this cohort may give further insight into the drug's exposure-response relationship and its associated inter-individual variability (IIV). The aim of this study was to assess the real-world PK of tezacaftor-ivacaftor in cwCF. Methods: A prospective, observational PK study was performed in cwCF using tezacaftor-ivacaftor. PK samples were obtained by dried blood spots (DBS) at home and during routine outpatient hospital visits. Population PK (popPK) models were created utilizing nonlinear mixed-effects modeling. Due to data scarcity, prior information from adolescent/adult PK models was required. Results: The study involved 21 children (age 6-17 years, weight 24-70 kg). Novel popPK models were created for tezacaftor-ivacaftor and its active metabolites. Variability in PK was explained by variation in body weight. The AUC of tezacaftor-ivacaftor varied significantly within and across age groups, which corresponded to the reported AUC in the product information. Cmax and elimination half-lives closely matched adult reported values. There was a strong correlation between Cmin and AUC for tezacaftor-ivacaftor. Conclusions: This is the first study to investigate the popPK of tezacaftor-ivacaftor in cwCF. The established models can be utilized for more personalized dosing in children experiencing suboptimal efficacy, adverse effects, drug-drug interactions, or where adherence is a concern.

Real-world population pharmacokinetics of tezacaftor-ivacaftor in children with cystic fibrosis: the SYM-CF study

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Principal Investigator Statement

The authors confirm that the Principal Investigator for this paper is Dr. E.M. Kemper and that she had direct clinical responsibility for patients.

Key words

Tezacaftor-ivacaftor

Cystic fibrosis

CFTR modulators

Population pharmacokinetics

Priors

Word, table, figure count

- Word count
- Manuscript body = 3767 (max. 4000 words)
- Abstract = 236 (max. 250 words)
- Tables = 4
- Figures = 4

Bullet point summary:

1. **What is already known about this subject** :
2. The clinical efficacy and safety of tezacaftor-ivacaftor in children with cystic fibrosis is highly variable in clinical practice.
3. Tezacaftor-ivacaftor has two fixed dosing regimens in children: [?]30kg receive the adult dose, and <30kg receive half of the adult dose.
4. A limited number of pharmacokinetic studies has been performed in children; data are sparsely published. No population pharmacokinetic data of tezacaftor-ivacaftor in children have been published so far.
5. **What this study adds** :
6. The first population pharmacokinetic models with real-world data were developed for tezacaftor-ivacaftor and its active metabolites using prior information from adolescents/adults.
7. AUC of tezacaftor-ivacaftor varied greatly within and across age groups; a strong correlation between C_{min} and AUC was observed.
8. The developed population pharmacokinetic models for tezacaftor-ivacaftor can be used in future studies evaluating the exposure-response relationship and its variability as a basis for more personalized dosing.

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Structured abstract

Aim : The clinical effectiveness of tezacaftor-ivacaftor in children with cystic fibrosis (cwCF) varies; some patients respond while others do not or have adverse effects. The pharmacokinetics (PK) of tezacaftor-ivacaftor are inadequately published, especially in children. Knowledge of the PK in this cohort may give further insight into the drug's exposure-response relationship and its associated inter-individual variability (IIV). The aim of this study was to assess the real-world PK of tezacaftor-ivacaftor in cwCF.

Methods : A prospective, observational PK study was performed in cwCF using tezacaftor-ivacaftor. PK samples were obtained by dried blood spots (DBS) at home and during routine outpatient hospital visits. Population PK (popPK) models were created utilizing nonlinear mixed-effects modeling. Due to data scarcity, prior information from adolescent/adult PK models was required.

Results : The study involved 21 children (age 6-17 years, weight 24-70 kg). Novel popPK models were created for tezacaftor-ivacaftor and its active metabolites. Variability in PK was explained by variation in body weight. The AUC of tezacaftor-ivacaftor varied significantly within and across age groups, which corresponded to the reported AUC in the product information. C_{max} and elimination half-lives closely matched adult reported values. There was a strong correlation between C_{min} and AUC for tezacaftor-ivacaftor.

Conclusions : This is the first study to investigate the popPK of tezacaftor-ivacaftor in cwCF. The established models can be utilized for more personalized dosing in children experiencing suboptimal efficacy, adverse effects, drug-drug interactions, or where adherence is a concern.

Background

Cystic fibrosis (CF) is an autosomal genetic disease, characterized by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. A mutation in this gene results in thick and sticky mucus, which impairs various organ functions including the lungs and pancreas. Until the early 2010s, therapy concentrated on airway clearance to remove mucus, pancreatic enzyme supplementation to aid digestion, and antibiotics to treat lung infections. The therapeutic management of people with CF (pwCF) is rapidly changing due to the emergence of highly effective modulator therapy. CFTR modulators are the first treatments for CF to address the fundamental cause of the disease. (1) Tezacaftor-ivacaftor was the second available combination of a CFTR corrector and a potentiator, respectively. In the Netherlands, tezacaftor-ivacaftor was approved in 2020 for children and adults from 12 years. In 2021 the approval was extended to children from 6-11 years. Tezacaftor-ivacaftor is registered for pwCF with a homozygous *F508del-mutation or* a heterozygous *F508del-mutation* , in combination with one of the 14 residual function mutations (P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A-G, S945L, S977F, R1070W, D1152H, 2789+5G-A, 3272-26A-G, and 3849+10kbC-T) which accounts for

Eligible children with CF (cwCF) start modulator treatment as soon as it becomes available for their age, and treatment is required indefinitely. At the moment of tezacaftor-ivacaftor introduction, children weighing 30kg or more receive the adult dose, while those weighing less than 30kg receive half the dose. (3) In real-life therapy response varies greatly, with some cwCF responding and some experiencing side effects. The pharmacokinetics (PK) appear to exert significant inter-individual variability (IIV), raising the possibility that specific patient groups are receiving dosages that are either too high or too low. Aside from that, tezacaftor-ivacaftor is susceptible to drug-drug interactions, since both components are substantially metabolized by cytochrome P450 3A4. This can lead to drug-drug interactions with for example –azole antifungals or rifampicin, which are commonly used by pwCF to treat infections. (3)

A limited number of PK studies has been performed in children. The only population PK (popPK) results available are those published in the registration documents, where data from adolescents (>12y) and adults are presented together. (4) In a phase 3 study conducted by the registration holder area under the curve (AUC) of tezacaftor-ivacaftor has been evaluated in children aged 6-11 years, but data are not presented in the publication. (5) Furthermore, there is currently a lack of independent studies evaluating the PK of tezacaftor-ivacaftor in children. Therefore, it is crucial to investigate the PK of tezacaftor-ivacaftor in

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children aged 6-17 years in real-world clinical settings. Even though most children have since switched to the newest triple therapy elexacaftor-tezacaftor-ivacaftor (ETI), this is still relevant since tezacaftor-ivacaftor are two of the three components in ETI. Gaining a deeper understanding of PK could improve knowledge of the exposure-response relationship and its associated IIV. This information may lead to better insights into drug efficacy and side effects and support the development of personalized dosing regimens.

Pediatric trials are often limited by the number of PK samples that can be collected, and traditional methods for PK analysis are not suitable. PopPK modelling methods can offer a solution in this case. However, because of the limited amount of data available, it is often not possible to precisely estimate all PK parameters of the model. Combining popPK methods with prior information from previous or adult models can improve the precision of the estimated PK parameters (6). The objective of this study is to describe the popPK of tezacaftor-ivacaftor and its active metabolites (tezacaftor-M1, ivacaftor-M1 and ivacaftor-M6) in cwCF using prior information. Secondary goals are to assess AUC,

maximum (C_{max}) concentration, and the elimination half-life ($t_{1/2}$) of tezacaftor and ivacaftor and the correlation between trough (C_{min}) concentration and AUC in this population.

Methods

Study design

Real-word data were prospectively collected in a multi-center, observational PK study in a cohort of 21 cwCF using tezacaftor-ivacaftor as chronic CF treatment. Between May 2021 and August 2022 cwCF were enrolled from three Dutch hospitals. Main inclusion criteria were children aged 6-17 years with at least one *F508del* -mutation, and the use of tezacaftor-ivacaftor according to regular care protocols: with tezacaftor-ivacaftor dosages of 100-300mg daily in children of [?]12 years and [?]6 years weighing [?]30kg, and 50-150mg in 6-11 years weighing deemed by the physician, and concomitant use of drugs with inhibitory or inducing effect on the CYP3A4 enzyme metabolism during 14 days before blood collection. The study was approved by the Institutional Review Board (ABR NL75811.018.21). Informed consent was obtained from all participants and their parents or legal guardians prior to any study-related procedures. Patients were included after a minimum of two weeks treatment with tezacaftor-ivacaftor, in order to reach steady-state concentrations. Patients were followed until they switched to elexacaftor-tezacaftor-ivacaftor. To facilitate PK sampling, patients and their parents were trained to perform dried blood spot (DBS) sampling. At one time point during the study, DBS samples were taken at home at T=0, 4 and 8 hours after administration of tezacaftor-ivacaftor by the participant/parent(s). During every regular visit at the outpatient clinic (˜every three months), a single sample was taken by venous or DBS sampling at a random time point after administration of tezacaftor-ivacaftor. No additional venipunctures were performed for PK analysis. Tezacaftor-ivacaftor administration and sampling times were recorded, as well as adherence (self-reported and physicians assessment) and the (fat) food with which tezacaftor-ivacaftor was taken. Clinical data as part of regular care were collected including patient demographics, CF-related co-morbidities, co-medication and liver function tests (ALAT, ASAT, bilirubin).

Sample preparation and analysis

DBS samples were stored at -20degC (after drying for a minimum of 30 minutes at room temperature) until analysis. DBS samples collected at home were sent to the hospital by mail in a sealed plastic bag and envelope. Venous blood samples were centrifuged and the plasma was stored at -80degC until analysis. The quantification of concentrations of tezacaftor, tezacaftor-M1, ivacaftor, ivacaftor-M1 and ivacaftor-M6 in plasma and DBS was performed using liquid chromatography-tandem mass spectrometry (LC-MS/MS), utilizing the method detailed in our previous publications. (7, 8) For all compounds the respective l**ower and upper limit of quantification (LLOQ/ULOQ) was 0.01 mg/L and 10 mg/L in plasma and DBS, except for tezacaftor-M1 (LLOQ 0.025 mg/L and ULOQ 12.5 mg/L). DBS concentrations were converted to their 'estimated plasma concentrations' (EPC) by the Passing-Bablok regression equation as described in our previous article. (8)**

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Population PK analysis using the PRIOR subroutine in NONMEM

In literature the PK of tezacaftor-ivacaftor has been described by two-compartment models (figure 1 and 2) (4, 9). In the present study, the available sparse data did not allow a precise estimation of all model PK parameters. Instead of fixing parameters to known values from the literature, the PRIOR subroutine was used in the nonlinear mixed-effects modelling (NONMEM) software (**v7.5.1 ICON Development Solutions, Dublin, Ireland**). (6) For development of the popPK models for tezacaftor-ivacaftor and their active metabolites, popPK information was derived from the registration document of tezacaftor-ivacaftor (Symdeko(r)). (4) In this document popPK parameters for tezacaftor, tezacaftor-M1 and ivacaftor models were described; no information was available for ivacaftor-M1/M6.

The PK of tezacaftor(-M1) was described by a two-compartment model for both the parent compound and the metabolite, with zero-order absorption into the depot compartment, followed by first order absorption to the central compartment and first-order elimination of both the parent and metabolite (figure 1). (4) The PK of ivacaftor was described by a two-compartment model for the parent compound with zero-order absorption into the depot compartment, followed by first order absorption to the central compartment. Elimination and conversion of the parent to the metabolites was described with first-order rate constants. (4) As there were no models available for ivacaftor's metabolites, they were described by a one-compartment model with first order absorption and elimination, and linked to the central compartment of ivacaftor (figure 2). (9, 10)

These models were used as a starting point for the popPK analysis of the current study. **Concentrations of the metabolites were adjusted to their parent equivalents using the molecular weight.** Since there is no intravenous formulation available, PK parameters of the parent compounds were estimated as apparent clearance (CL/F), apparent intercompartmental clearance (Q/F) and apparent volume of distribution (V/F). For the metabolites the fraction parent drug metabolized into the metabolite was fixed to 1, and therefore PK parameters of the metabolites were estimated as apparent clearance of the fraction metabolized ($CL/(F*f_m)$) and apparent volume of distribution of the fraction metabolized ($V/(F*f_m)$).

Ας τηερε ωας α ωιδε ρανγε ιν βοδψ ωειγητ (BΩ), αλλομετρις σχαλινγ φορ BΩ ωας αππλιεδ ον ϑΛ/Φ(*φ_μ), X/Φ(*φ_μ) ανδ ″/Φ(*φ_μ) (Εχ. 1 ανδ 2). Ωηερε ϑ ις τηε τψπιχαλ εστιματε φορ ϑΛ, X, ″$_\varsigma$ ανδ ″$_\pi$, νορμαλιζεδ φορ α βοδψ ωειγητ οφ 70 κγ.

Equation 1 $\frac{CL/Q}{F(*f_m)} = \theta_{CL/Q} * \left(\frac{BW}{70}\right)^{0.75}$

Equation 2 $\frac{V}{F(*f_m)} = \theta_V * \left(\frac{BW}{70}\right)^{1}$

IIV was assessed on CL (Eq. 3). Where **η$^{\vartheta}_{\Lambda}$ ις α νορμαλλψ διστριβυτεδ ρανδομ αριαβλε ωιτη α μεαν οφ ζερο ανδ αν εστιματεδ αριανχε οφ ω^2, ινδιχατινγ τηε ΙΙ″ ιν ϑΛ.**

Equation 3 $CL = \theta_{CL} * e^{\eta_{CL}}$

Ρεσιδυαλ αριαβιλιτψ ωας ασσεσσεδ βψ τεστινγ προπορτιοναλ, αδδιτιε ανδ χομβινεδ ερρορ μοδελς το δεσχριβε διφφερενχες βετωεεν ινδιιδυαλ πρεδιχτιονς ανδ οβσερατιονς (Εχ. 4). Ωηερε ϑ ις τηε τψπιχαλ εστιματε φορ τηε προπορτιοναλ ορ αδδιτιε ερρορ, ΙΠΡΕΔ ις τηε ινδιιδυαλ πρεδιχτεδ χονχεντρατιον ανδ Ψ ις τηε μοδελλεδ αλυε οφ τηε οβσερεδ αριαβλε.

Equation 4 $Y = \text{IPRED}\ (1 + \theta_{prop}) + \ \theta_{add}$

For ivacaftor-M1 and M6 separate proportional error models for plasma and DBS samples were implemented.

In order to define the weight of the prior value of the PK parameters, predefined residual standard error (RSE) values were used. Three types of prior weight were predefined and based on numbers described in literature: informative (10% RSE), moderately informative (30% RSE) and weakly informative/vague (10^5). (6) The first step was to assign informative priors on all parameters, except for CL, IIV and the residual error. No priors were assigned to CL, as data were thought to be rich enough to estimate this parameter without a prior. Also, as described above IIV was only applied on CL and no priors were used to estimate

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the IIV on other PK parameters. As well as the residual error, which was also estimated without priors on basis of the available data.

The next step was to change one parameter at the time to a vague prior, and assess whether this parameter could be estimated on basis of the available data – with weakly prior information. If estimation was not possible, the following step was to change this parameter to a moderate informative prior. If estimation was still not possible, the parameter was set to the informative prior again. These steps were repeated for all parameters in order to obtain a stable structural model, which was defined by being able to estimate the model parameters with a value within an expected range with a maximum RSE of 30%.

Following the development of the structural model, a covariate analysis was conducted to determine whether covariates could explain IIV. A covariate search can only be applied on parameters without a prior, in this case CL. (6) The covariates assessed included age, adherence and CF mutation. **Stepwise forward inclusion was used in the covariate analysis. A reduction in objective function value (OFV) [?]3.81 (P=0.05) was considered statistically significant. Dichotomous and continuous covariates were included in the model (Eq. 5 and 6). In this context, $_{i}$ represents the individual model predicted PK parameter for an individual with covariate value cov_i. $_{pop}$ is the population estimate for that parameter, cov_m is the median covariate value and $_{cov}$ denotes the covariate effect.**

Equation 5$\theta_i = \theta_{\text{pop}} * \theta_{\text{cov}}{}^{\text{cov}_i}$

Equation 6$\theta_i = \theta_{\text{pop}} * (\frac{\text{cov}_i}{\text{cov}_m})^{\theta_{\text{cov}}}$

The first-order conditional estimation with interaction (FOCE-I) in NONMEM was used for all runs.

The m**odel fits were based on visual inspection of goodness-of-fit (GOF) plots, OFV, parameter precision, and shrinkage values. The robustness of the parameter estimates and the validity of the models were evaluated with a bootstrap analysis (n=1000) and a visual predictive check (VPC), respectively. Data handling, visualization and descriptive statistics were performed using Pirana**

(v2.9.4 Certara, Radnor, PA, USA), R Studio version 4.3.1 and GraphPad Prism 9.0 (GraphPad Software, Boston, Massachusetts, USA).

AUC, C_{max}, and elimination half-life of tezacaftor-ivacaftor real-world compared to reported values

AUC$_{0\text{-}24\eta}$ φορ τεζαςαφτορ(-M1) ανδ AUC$_{0\text{-}12\eta}$ φορ ιαςαφτορ(-M1 ανδ –M6), C_{max}, ανδ τερμιναλ ελιμινατιον ηαλφ-λιφε ($\tau_{1/2,\beta}$) ωερε ασσεσσεδ δυρινγ εερψ οςςασιον βψ Βαψεσιαν αναλψσις. Τηε οβταινεδ αλυες ωερε ςομπαρεδ το τηειρ ρεπορτεδ αλυες ας δεσςριβεδ ιν τηε προδυςτ ινφορματιον. (3)

Correlation between C_{min} and AUC

In order to evaluate the correlation between C_{min} and AUC, the measured C_{min} for tezacaftor (>20h after dose) and ivacaftor (>10h after dose) were compared with the estimated **AUC$_{0\text{-}24h}$ and AUC$_{0\text{-}12h}$, respectively.** Pearson's r was used to evaluate the correlation between C_{min} and AUC.

Results

Population and data characteristics

In total 21 patients were included in the study, contributing to a total of 97 PK samples (13 plasma samples and 84 DBS samples). Results from three (3%) samples were excluded due to incorrect DBS sampling (1), and missing dosing information (2). Ivacaftor-M6 concentration in 3 samples (3%) was below the LLOQ and excluded. No samples were above the ULOQ.

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Patient demographics and baseline characteristics are summarized in table 1. All patients used tezacaftor-ivacaftor according to the dose recommendation as stated in the product information. (3)

Population pharmacokinetic analysis

Tezacaftor and tezacaftor-M1

In table 2 the estimated PK parameters of the final models of tezacaftor and its M1-metabolite are shown. The most stable model was created with a vague prior on $V_{c\ tez}$, with moderate informative priors on $V_{p\ tez}$, Q_{tez}, D1 and $Q_{tez\text{-}M1}$, and with informative priors on KA, $V_{c\ tez\text{-}M1}$ and $V_{p\ tez\text{-}M1}$. No prior information was applied on CL and its IIV, as the data were rich enough to estimate these parameters. No correlations of the covariates age, CF mutation or adherence were observed on CL.

Ivacaftor, ivacaftor-M1 and ivacaftor-M6

In table 2 the estimated PK parameters of the final models of ivacaftor (-M1/6) are shown. Values for $V_{iva\text{-}M1}$ and $V_{iva\text{-}M6}$ were fixed at $0.1*V_{iva}$, as we were unable to estimate them and no popPK models have been described for the metabolites in literature. A factor of 0.1 was chosen because basic lipophilic drugs such as ivacaftor often have a large V (>100L), whereas their more polar and acidic metabolites have volumes closer to 10 of 20L. (11) For ivacaftor-M6 the proportional error (RSE) in plasma samples was larger than DBS samples with values of 0.98 (225%) and 0.50 (10%), respectively. The most stable model was created with a vague prior on $V_{c\ iva}$, with moderate informative priors on $V_{p\ iva}$ and Q_{iva}, and with informative priors on KA and D1. No prior information was applied on CL and its IIV, as the data were rich enough to estimate these parameters. No correlations of the covariates age, CF mutation or adherence were observed on CL.

Model evaluation

RSE values of estimated parameters were generally low both for the typical PK parameters *([?]29%) and the random effects (IIV on CL [?]38%). GOF plots (appendix – figure A1-3) and VPC plots (figure 3) demonstrate that the developed models adequately describe the observations. The robustness of the models was evaluated by a bootstrap analysis; its results are presented in* table 2.

AUC, C_{max}, and half-life of tezacaftor-ivacaftor real-world compared to reported values

In table 3 the average AUC values per age and dosing group are shown and compared with the corresponding reported value in the product information. (3) The variability is large within age groups, as demonstrated by the large SD with corresponding coefficients of variation (CV) between 16-88%. The AUC differs per age group, as children 6-11y [?] 30kg tend to have a higher AUC value than children from other age groups. Difference in average AUC versus reported values in the product information was less than ±17%, except for tezacaftor in 12-17y and ivacaftor in 6-11y [?] 30kg with -32% and 48% difference, respectively.

In table 4 mean (SD) C_{max} and half-lives per age and dosing group are presented for tezacaftor-ivacaftor in relation to their reported adolescent/adult values in the product information and registration document. (3, 4) Children with age 6-11y with a body weight [?]30kg tend to have a higher mean C_{max}, and in the age group 6-11y < 30kg the mean half-lives tend to be shorter. Overall the pooled mean C_{max} seems slightly lower for tezacaftor in our pediatric data, compared to the reported adult values. (3) For tezacaftor the half-lives in children tend to be shorter compared to the reported adult values. (3) For ivacaftor C_{max} are overall comparable and half-lives tend to be higher than the reported values in adults, except for the age group 6-11y < 30kg. (3)

Correlation between C_{min} and AUC

Median (range) measured C_{min} concentrations were 1.3 (0.47-4.8) mg/L and 0.73 (0.28-2.4) mg/L for tezacaftor and ivacaftor, respectively. A linear correlation was seen (figure 4) between observed C_{min} and the calculated $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}12h}$, with Pearson's r correlation coefficients of 0.931 and 0.942 for tezacaftor and ivacaftor, respectively. The variance of AUC could for 87% and 89% be explained by C_{min} for tezacaftor and ivacaftor determined by R^2, respectively.

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Discussion

In this study, popPK models for tezacaftor-ivacaftor and its active metabolites were successfully developed in children with real-world data using prior information from adolescent/adult models. Substantial variability in AUC was observed both within and across age and dosing groups. In general, AUC corresponded well with reported values in the product information, except for tezacaftor in 12-17y and ivacaftor in 6-11y[?]30kg. C_{max} and half-lives also corresponded closely with reported values, though in children 6-11y[?]30kg C_{max} tended to be higher and in children 6-11y<30kg half-lives tended to be shorter. (3) Also, a strong correlation between C_{min} and AUC was found for tezacaftor-ivacaftor.

Although in this study sparse data was available, the prior subroutine was essential to successfully develop full popPK models, that also described the absorption phase and the distribution to peripheral compartments. It was not possible to obtain these extended models without prior information, emphasizing the importance of prior information in popPK modeling when data are limited, as is frequently the case in pediatric studies. When data are sparse, there are two methods to stabilize difficult-to-estimate parameters: 1. Fix them to a previous value described in literature; 2. 'Inform' them about the previous values. The latter strategy minimized bias in situations where the parameters differed somewhat between the preceding population and the population from which the sparse data were taken. (6)

The key covariate of relevance for this analysis was weight as predictor of **CL/F(*f_m), Q/F(*f_m) and V/F(*f_m), and was pre-defined. This is fairly typical in pediatric studies due to the large weight range, partially explaining the IIV in PK parameters.** No other covariates explaining IIV were identified, likely due to the study being underpowered for this type of analysis. Interestingly, despite the real-world context, AUC variability in our studies (CV=16-88%) was in close agreement with the reported values in the product information. (3) A notable contribution of this study is the first real-world AUC data for children in the 30-40 kg weight class, as the registration studies relied on model-based predictions in this weight group due to other weight-dose group categorizations. (3, 5) Additionally, our findings of elevated AUC and C_{max} in children 6-11y[?]30kg raise questions about whether the tezacaftor-ivacaftor dose is appropriate for all children within this subgroup, as they receive the adult dose. Lowering the dose could reduce the risk of overexposure and possible development of side effects, as well as saving costs. The observation of a consistent relationship between C_{min} and AUC in both this study and our previous work in adults, suggests that C_{min} could be a valuable predictor of AUC for TDM in this population. (12)

This study benefits from several strengths, including the use of real-world data in children 6-17y that allowed the analysis of AUC in the 30-40 kg weight class, where limited data previously existed. Also, real-world PK data are relevant to account for the difference between controlled clinical trials and the complexity of drug use in diverse, every day settings. Next, the selective use of informative prior information from adolescents/adults was used to support portions of the model that were not well defined from the currently available pediatric data (Ka, D1, V_p, Q) and allowed for the estimation of the remaining parameters (CL, V). Limited sampling strategies were applied to reduce the burden of PK sampling in this age group. As well as the use of DBS sampling (at home), which served as a feasible PK sampling method and patients experienced this as less invasive than a venipuncture. (8) Especially in the era of changing CF care this method is preferable, as pwCF have better outcomes and will probably visit the hospital less frequent. (13) Furthermore, intake with fatty food was registered, which allowed for additional control over factors influencing drug absorption as fatty food increases the absorption of tezacaftor-ivacaftor. (3) Concomitant fatty food intake was not further investigated in the covariate analysis, as the absorption parameters were estimated with prior information and covariates can only be applied on parameters estimated without priors. (6)

Despite this, the study has some limitations. The sample size was small, due to faster access to ETI than expected, which limited the recruitment as some children did not start with tezacaftor-ivacaftor awaiting ETI. This also immediately implies that tezacaftor-ivacaftor is hardly used, since the introduction of ETI. However, the findings in this study are still useful because elexacaftor had little effect on the PK of tezacaftor-ivacaftor, as indicated in the registration report. (4) Furthermore, due to the short study duration, only

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one AUC curve was acquired for certain patients who used home-based DBS collections. This also resulted in incomplete covariate data in those patients (e.g. liver-enzyme measurements), as they did not visit the hospital during the study visit. This could have resulted in an underpowered covariate analysis, prohibiting a thorough assessment of the IIV in PK of tezacaftor-ivacaftor. This also made it impossible to assess the inter-occasion variability. Last, self-reported adherence could have influenced the results of the study, however this reflects a real-world situation.

To conclude, this study is the first to describe the popPK of tezacaftor-ivacaftor and its active metabolites in cwCF based on real-world data. The selective use of prior information from adolescent/adult models enabled the development of stable and robust models. The popPK models developed in this study could be used as a basis for more personalized medicine. Future applications of such TDM models could enhance dose optimization, particularly for children experiencing suboptimal efficacy, adverse effects, drug-drug interactions, or where adherence is a concern.

Acknowledgements

The authors would like to thank all patients and their parents for their participation in this study. The authors also would like to thank Simone Tanner-Winkel, Hilda Vale-Eeman, Irma Bon, Faiza Wester, Badies Manai and Joel Israels for their specific contributions to this study.

Conflict of interest statement

The authors have no conflict of interest to declare.

Funding information

No funding.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its appendices. Raw data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Figure legends

Figure 1 *– Schematic illustration of the pharmacokinetic model of tezacaftor and its main metabolite tezacaftor-M1. Abbreviations: D1; zero-order absorption into the gut compartment, KA; absorption rate constant, $V_{c\ TEZ}/F$; apparent tezacaftor central volume of distribution, $V_{p\ TEZ}/F$; apparent tezacaftor peripheral volume of distribution, Q/F; apparent intercompartmental clearance, CL_{TEZ}/F; apparent tezacaftor clearance, $V_{c\ M1}/(F*f_m)$; apparent tezacaftor-M1 central volume of distribution of the fraction metabolized, $V_{p\ M1}/(F*f_m)$; apparent tezacaftor-M1 peripheral volume of distribution of the fraction metabolized, $CL_{M1}/(F*f_m)$; apparent tezacaftor-M1 clearance of the fraction metabolized, Q_m/f_m; intercompartmental clearance of the fraction metabolized.*

Figure 2 *– Schematic illustration of the pharmacokinetic model of ivacaftor and its main metabolites ivacaftor-M1 and ivacaftor-M6. Abbreviations: D1; zero-order absorption into the gut compartment, KA; absorption rate constant, $V_{c\ IVA}/F$; apparent ivacaftor central volume of distribution, $V_{p\ IVA}/F$; apparent ivacaftor peripheral volume of distribution, Q/F; apparent intercompartmental clearance, CL_{IVA}/F; apparent ivacaftor clearance, $V_{c\ M1/6}/(F*f_m)$; apparent ivacaftor-M1/6 central volume of distribution of the fraction metabolized, $CL_{M1/6}/(F*f_m)$; apparent ivacaftor-M1/6 clearance of the fraction metabolized, Q_m/f_m; intercompartmental clearance of the fraction metabolized.*

Figure 3 – Prediction corrected visual predictive checks (VPC) of the final models. The open circles represent the prediction correct concentrations of tezacaftor, tezacaftor-M1, ivacaftor, ivacaftor-M1 and ivacaftor-M6. The solid black line represents the observed median and the dashed black lines represent the 5^{th} and 95^{th} percentiles of the observed prediction-corrected data. The blue areas represent the 80% confidence interval of the model-predicted 5^{th} and 95^{th}percentiles. The orange area represents the 80% confidence interval of the model-predicted median. For tezacaftor, tezacaftor-M1, ivacaftor and ivacaftor-M6, the solid black line slightly rises above the orange shaded area at the end of the dosing interval, indicating a minor underestimation of the observed 50^{th} percentile. For ivacaftor-M1, the dashed black line slightly rises above the blue shaded area at the beginning of the dosing interval, indicating a minor underestimation of the observed 5^{th} percentile. For ivacaftor-M6, the dashed black line slightly rises above the blue shaded area in the middle of the dosing interval, indicating a minor underestimation of the observed 95^{th} percentile.

Figure 4 – $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}12h}$ versus C_{min} for tezacaftor and ivacaftor. Tezacaftor Pearson's r = 0.931 (95% CI = 0.837 – 0.971, P<0.0001), R^2 = 0.866, regression equation: y=20.68x+37.48. Ivacaftor Pearson's r = 0.942 (95% CI = 0.848 – 0.979, P<0.0001), R^2 = 0.887, regression equation: y=9.14x+5.69.

AUC, area under the curve; C_{min}, trough concentration; CI, confidence interval.

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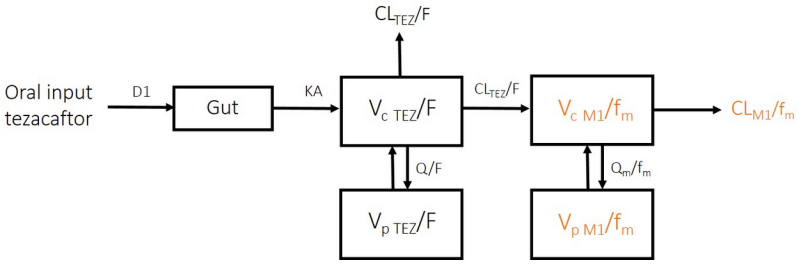

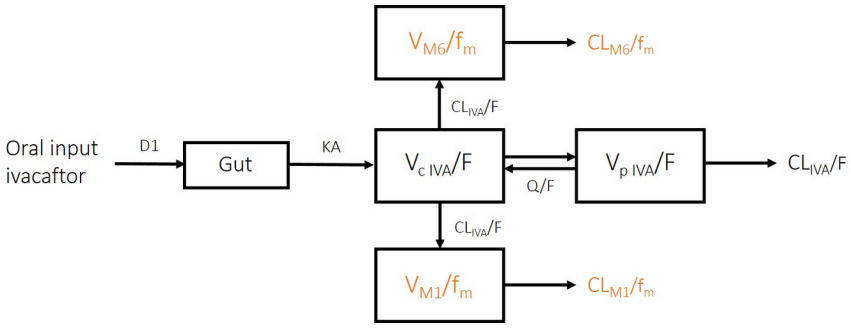

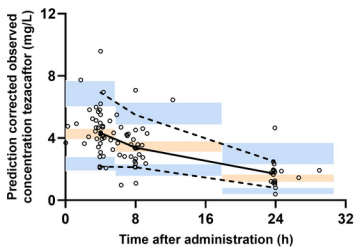

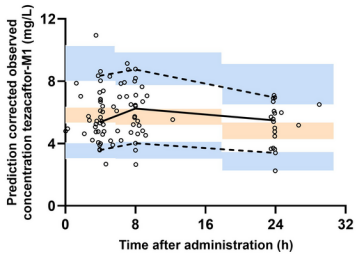

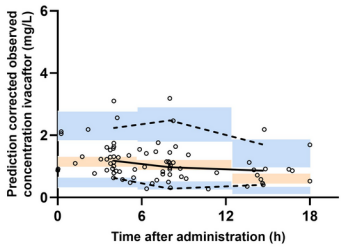

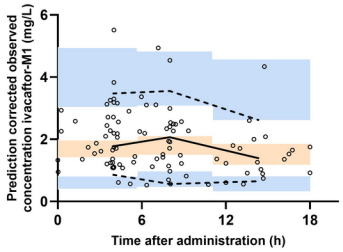

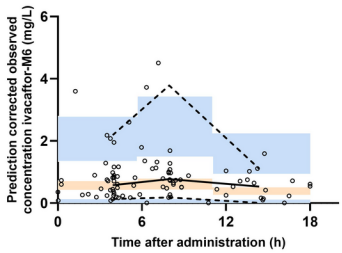

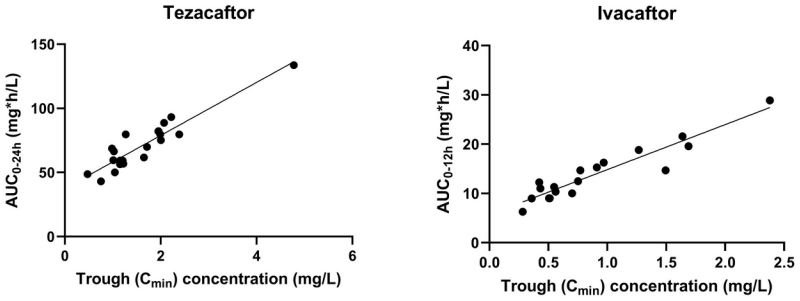

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