Physiologically-Based Pharmacokinetic-Led Guidance for Patients With Cystic Fibrosis Taking Elexacaftor-Tezacaftor-Ivacaftor With Nirmatrelvir-Ritonavir for the Treatment of COVID-19

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Cystic fibrosis transmembrane conductance regulator (CFTR) modulating therapies, including elexacaftor-tezacaftor-ivacaftor, are primarily eliminated through cytochrome P450 (CYP) 3A–mediated metabolism. This creates a therapeutic challenge to the treatment of coronavirus disease 2019 (COVID-19) with nirmatrelvir-ritonavir in people with cystic fibrosis (CF) due to the potential for significant drug–drug interactions (DDIs). However, the population with CF is more at risk of serious illness following COVID-19 infection and hence it is important to manage the DDI risk and provide treatment options. CYP3A-mediated DDI of elexacaftor-tezacaftor-ivacaftor was evaluated using a physiologically-based pharmacokinetic modeling approach. Modeling was performed incorporating physiological information and drug-dependent parameters of elexacaftor-tezacaftor-ivacaftor to predict the effect of ritonavir (the CYP3A inhibiting component of the combination) on the pharmacokinetics of elexacaftor-tezacaftor-ivacaftor. The elexacaftor-tezacaftor-ivacaftor models were verified using independent clinical pharmacokinetic and DDI data of elexacaftor-tezacaftor-ivacaftor with a range of CYP3A modulators. When ritonavir was administered on Days 1 through 5, the predicted area under the curve (AUC) ratio of ivacaftor (the most sensitive CYP3A substrate) on Day 6 was 9.31, indicating that its metabolism was strongly inhibited. Based on the predicted DDI, the dose of elexacaftor-tezacaftor-ivacaftor should be reduced when coadministered with nirmatrelvir-ritonavir to elexacaftor 200 mg–tezacaftor 100 mg–ivacaftor 150 mg on Days 1 and 5, with delayed resumption of full-dose elexacaftor-tezacaftor-ivacaftor on Day 9, considering the residual inhibitory effect of ritonavir as a mechanism-based inhibitor. The simulation predicts a regimen of elexacaftor-tezacaftor-ivacaftor administered concomitantly with nirmatrelvir-ritonavir in people with CF that will likely decrease the impact of the drug interaction.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy, elexacaftor-tezacaftor-ivacaftor, is primarily eliminated through cytochrome P450 3A4 (CYP3A4)–mediated metabolism, creating a therapeutic challenge in people with cystic fibrosis (CF) due to the potential for significant drug–drug interactions (DDIs).

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Dosing guidelines for elexacaftor-tezacaftor-ivacaftor in people with CF receiving treatment with nirmatrelvir-ritonavir for coronavirus disease 2019 (COVID-19).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The study provides physiologically-based pharmacokinetic (PBPK) tools to evaluate clinically important DDIs involving elexacaftor-tezacaftor-ivacaftor. Through simulations, this study identified the need for a significant dose reduction in elexacaftor-tezacaftor-ivacaftor that will likely decrease the impact of a drug interaction with nirmatrelvir-ritonavir.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The use of PBPK modeling and simulation to address new drug interactions provides timely guidelines for dose adjustment where clinical trial data do not yet exist. In particular, PBPK modeling allows determination of dosing during transitions where an interacting drug is added or discontinued. This is especially needed in the case of a mechanism-based inhibitor, where there is delayed recovery of inhibitory effect after discontinuation of the inhibitor.

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The introduction of the cystic fibrosis transmembrane conductance regular (CFTR) modulator, a triple combination of elexacaftor-tezacaftor-ivacaftor (Trikafta) has resulted in significant improvements in lung function and nutritional status in people with cystic fibrosis.[1] While elexacaftor-tezacaftor-ivacaftor is indicated in up to 90% of the CF population,[1] all three components are eliminated mainly through cytochrome P450 (CYP) 3A-mediated hepatic metabolism,[2] and therefore present a therapeutic challenge in people with CF due to the potential for significant drug–drug interactions (DDIs). The use of strong CYP3A inducers will increase the metabolism of elexacaftor-tezacaftor-ivacaftor, resulting in reduced exposure and a potential lack of efficacy, while concomitant therapy with agents that inhibit CYP3A will increase elexacaftor-tezacaftor-ivacaftor levels, placing the patient at increased risk of adverse effects (AEs), including respiratory-related AEs and abnormal liver function tests. Therefore, the safe and effective use of CFTR modulators requires appropriate DDI management with concomitant CF medications.

One notable therapeutic challenge is in the treatment of coronavirus disease 2019 (COVID-19) (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)). In people with CF, viral respiratory tract infections can lead to acute pulmonary exacerbations with a negative impact on lung function.[3] COVID-19 infection triggers a cytokine storm which can lead to the life-threatening respiratory distress syndrome, potentially putting the population with CF infected with COVID-19 at high risk of serious illness.[4] The US Food and Drug Administration (FDA) has recently issued an emergency use authorization for the use of the nirmatrelvir-ritonavir (Paxlovid) for the treatment of mild to moderate COVID-19. Nirmatrelvir-ritonavir treatment significantly reduces hospital admissions and deaths among people with COVID-19 who are at high risk of severe illness.[5] Nirmatrelvir is coadministered with ritonavir, a CYP3A inhibitor, to boost nirmatrelvir concentrations to achieve therapeutic levels.[5] However, due to the potent inhibition effect of ritonavir, it may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Therefore, coadministration of nirmatrelvir-ritonavir is contraindicated with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. Since all three components of elexacaftor-tezacaftor-ivacaftor are eliminated mainly through CYP3A, nirmatrelvir-ritonavir is expected to exhibit a significant drug interaction with elexacaftor-tezacaftor-ivacaftor. Thus, the use of nirmatrelvir-ritonavir in people with CF would require an adjusted dosing regimen of elexacaftor-tezacaftor-ivacaftor to prevent increased plasma concentrations and potential adverse drug reactions. However, there are currently no clinical data available regarding the interactions of elexacaftor-tezacaftor-ivacaftor with nirmatrelvir-ritonavir, and no specific dosing guidelines have been established. Therefore, there is an urgent need for the proper guidance regarding the use of nirmatrelvir-ritonavir for people with CF to prevent progression of COVID-19 to severe disease.

This study aimed to investigate the magnitude of the drug interactions of ritonavir-elexacaftor-tezacaftor-ivacaftor, to simulate possible treatment scenarios and provide dosing recommendations to overcome the interaction. The CYP3A inhibition-mediated drug interaction of elexacaftor-tezacaftor-ivacaftor was evaluated using a physiologically-based pharmacokinetic (PBPK) simulation-based approach. PBPK simulation is a tool to predict the pharmacokinetic behavior of drugs in humans by integrating the information from multiple *in vitro* and clinical studies, exploring the effects of drug (e.g., physicochemical properties) and system (e.g., physiological) information on drug exposure. The predictive performance of PBPK simulations for CYP enzyme-based DDIs has been well established,[6,7] and this strategy is increasingly included during regulatory review by the FDA as an alternative for exploring DDI potential to provide dosing recommendations in the product labeling.[8] The present study contributes to improved treatment for COVID-19 in people with CF by providing tools to evaluate and potentially overcome clinically important drug interactions involving highly active CFTR modulator therapy.

METHODS

The workflow adopted for PBPK model development, verification, and application are illustrated in **Figure 1**. The models were implemented within the Simcyp Simulator (version 19; Certara, Sheffield, UK).

Model development

Population model. In the default healthy population library file (Sim-Healthy volunteers) provided in Simcyp, the distribution of ages and proportion of females were corrected to reflect the demographics of the population with CF based on the Patient Registry 2020 Annual Data Report published by the Cystic Fibrosis Foundation.[9] Specifically, the frequency in the population aged 18–21 years, was adjusted from 4.5% in the healthy population to 13.1% in CF. Also, the proportion of females was adjusted from 0.32 in the healthy population to 0.48 in CF. The mean body mass index (BMI) of the healthy population (23.5 kg/m^2) was similar to that observed in CF (21.2 kg/m^2 in 2005 to 23.1 kg/m^2 in 2020) and no further adjustment was needed, reflecting how BMI in the population with CF has been increased over the years with continued improvements in CF care.[9,10] All other system parameters were kept as the default healthy, and this assumption is in line with the pharmacokinetic (PK) parameters of elexacaftor-tezacaftor-ivacaftor not differing between healthy adults and people with CF.[11–13] This population library file was used for all simulations. For trial design, we used a total size of 100 population (10 trials and 10 participants in each trial).

PBPK model of ivacaftor. The model input parameters for ivacaftor are summarized in **Table S1**. The ivacaftor model consists of the advanced dissolution, absorption, and metabolism model and minimal PBPK model. It was constructed based on available physicochemical properties and clinical data from published PK studies.[11,14–17] The *in vitro* studies and clinical DDI data suggest that ivacaftor is predominantly eliminated through CYP3A4-mediated hepatic metabolism.[13] Therefore, the excretion was set to enzyme kinetics to quantify its metabolism by CYP3A. The intrinsic clearance by

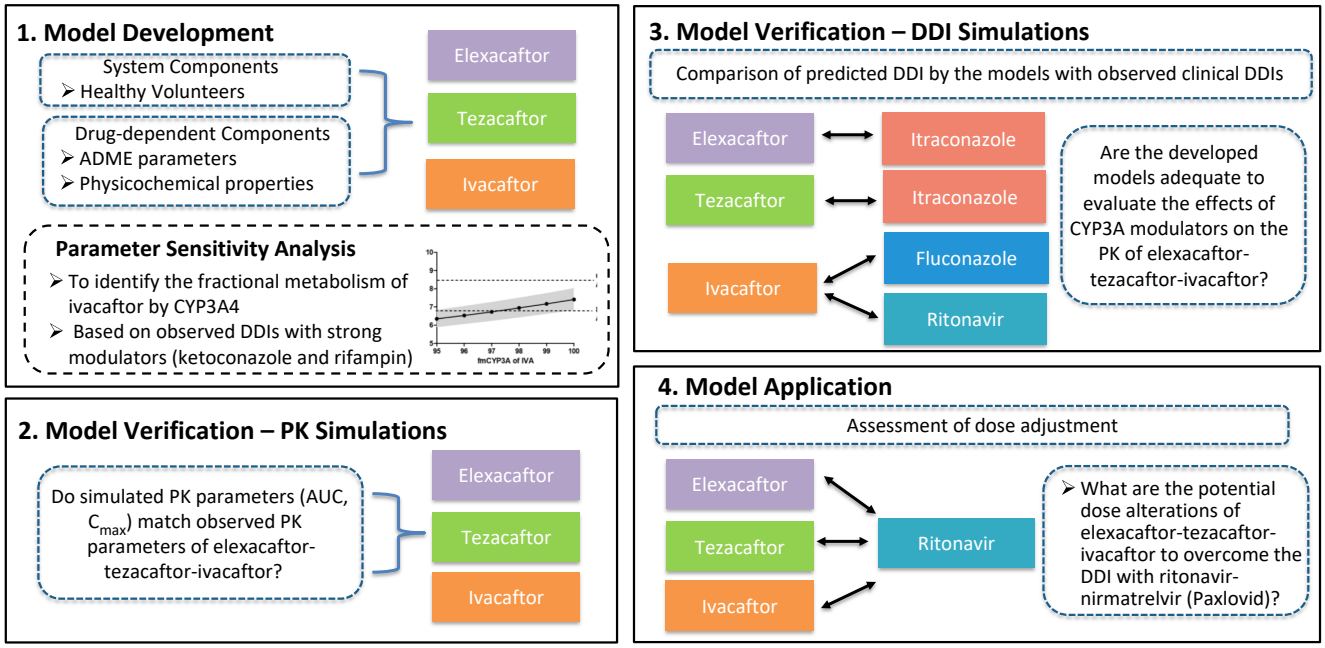

Figure 1 PBPK modeling framework detailing the processes of model development and verification that were performed in this study. Successful model verification must precede the application of the PBPK model of elexacaftor-tezacaftor-ivacaftor for predictions of drug interactions with nirmatrelvir-ritonavir. ADME, absorption, distribution, metabolism, and elimination; AUC, area under the curve; C_{max}, maximum plasma concentration; CYP3A4, cytochrome P450 3A4; DDIs, drug–drug interactions; PK, pharmacokinetic. [Colour figure can be viewed at wileyonlinelibrary.com]

CYP3A4 was back calculated from the oral clearance observed in healthy participants (19.0 L/hours).[11] The fraction of ivacaftor being metabolized by CYP3A4 (fmCYP3A4) was set to 98% in order to capture the observed drug interactions of ivacaftor with the strong CYP3A4 modulators, ketoconazole or rifampin. The fraction escaping gut-wall elimination was also optimized to 0.50 using observed DDI data. Sensitivity analysis around key parameters (fmCYP3A4, fraction escaping gut-wall elimination, and fraction unbound in the enterocyte) conferring DDI liability was carried out and confirmed that the values used provided the most robust model for prediction of the maximum plasma concentration (C_{max}) and area under the curve (AUC) responses observed in the clinical data (data not shown).

PBPK models of tezacaftor and elexacaftor. The model input parameters for tezacaftor and elexacaftor are summarized in **Tables S2–S3**. The models were constructed based on the data from the PBPK review section within the New Drug Application (NDA) documents and the publication of Tsai *et al.*[12,13,15] Briefly, the models consist of the first-order absorption and a minimal PBPK model. In the NDA document, it was described that the absorption and distribution parameters were obtained from the observed PK profiles following clinical phase I–III studies, and the fmCYP3A4 of elexacaftor and tezacaftor were set to 67% and 73.2% based on human absorption, distribution, metabolism, and elimination studies. Using the retrograde model, the intrinsic clearance of elexacaftor and tezacaftor attributed to CYP3A4 were calculated to be 0.233 and 0.175 μL/minutes per picomole of isoform. The M1-tezacaftor, active metabolite of tezacaftor, was also incorporated into the tezacaftor PBPK model based on data in the NDA document.[12] The other active metabolites, M23-elexacaftor and M1-ivacaftor, were not incorporated into the PBPK analyses due to insufficient information to build the model.

PBPK models of CYP3A modulators. Rifampin, ketoconazole, fluconazole, itraconazole, and its primary metabolite, hydroxy itraconazole, are prototypical CYP3A modulators that have been implicated in clinical drug interaction studies with elexacaftor, tezacaftor, or ivacaftor. Ritonavir is also a CYP3A modulator for which we aimed to predict interactions with elexacaftor-tezacaftor-ivacaftor. For simulation of DDIs, the validated compound files of these CYP3A modulators provided in Simcyp (version 19) were used.

Model verification: PK simulations

The PK profiles of elexacaftor-tezacaftor-ivacaftor following a single oral dose administration and multiple administrations of clinically relevant doses (elexacaftor 200 mg once daily (q.d.), tezacaftor 100 mg q.d., and ivacaftor 150 mg every 12 hours (q12h)) were first simulated to verify the performance of the PBPK models. Exacaftor-tezacaftor-ivacaftor was orally administered under fed conditions to mimic the clinical setting, where the fat-containing food is required for optimal absorption of elexacaftor-tezacaftor-ivacaftor. The simulated data were qualified using the observed PK data in a population with CF aged older than 17 years. The prediction accuracy for the AUC and C_{max} values were calculated as a ratio of mean observed values over mean predicted values. Successful model performance was defined by mean ratios of AUC and C_{max} within a twofold range as previously described.[18,19] Although the therapeutic window of elexacaftor-tezacaftor-ivacaftor has not been clearly defined, CFTR modulators were generally well tolerated in clinical trials with no dose-related safety concerns identified.[1,20]

Model verification: DDI simulations

Upon accurate recapitulation of the PK of elexacaftor-tezacaftor-ivacaftor, the models were further assessed against the clinical DDI data to verify fmCYP3A4 and establish whether the models were adequate for the assessment of victim DDI liability. For verification simulations, the dose and schedule of drugs were matched to the design of the corresponding clinical DDI studies in healthy participants.[11–13,21] To quantify the DDIs, the geometric mean ratios of AUC or C_{max} with or without

the presence of CYP3A4 modulators were calculated. The assessment of DDI prediction success was based on whether predictions were within a twofold range of the observed data.

Model application: DDI predictions of elexacaftor-tezacaftor-ivacaftor with ritonavir

Although ritonavir-nirmatrelvir is a fixed dose combination of two drugs, nirmatrelvir was not included in the simulations as there is no clinical evidence that it modulates CYP3A4 activity. The verified PBPK-DDI model was applied to (i) predict the effect of ritonavir on the PK of elexacaftor-tezacaftor-ivacaftor and (ii) determine a potential dose alteration of elexacaftor-tezacaftor-ivacaftor to overcome the CYP3A inhibition mediated by ritonavir. We first simulated the steady-state PK of standard dose elexacaftor-tezacaftor-ivacaftor alone and when coadministered with 100 mg ritonavir twice daily for 5 days based on the instruction for dosage and administration in the FDA-approved fact sheet of nirmatrelvir-ritonavir.[5] In addition, since ritonavir acts as a mechanism-based CYP3A4 inhibitor by covalently binding to CYP3A4,[22] simulations were run until CYP3A4 and the PK of elexacaftor-tezacaftor-ivacaftor had returned to baseline (10 days after ritonavir discontinuation). We then simulated several adjusted dosing regimens of elexacaftor-tezacaftor-ivacaftor (elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg q72h and q96h, and elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg q48h) when coadministered with ritonavir to find the regimen that could provide the closest PK profiles of standard dosing of elexacaftor-tezacaftor-ivacaftor alone. The dosing regimen was optimized to target an AUC over the dosing interval (AUC_{tau}) of elexacaftor and tezacaftor within the bioequivalence limit (0.80–1.25) and AUC_{tau} of ivacaftor within 1.5-fold relative to the standard regimen.

RESULTS

Development and verification of the elexacaftor-tezacaftor-ivacaftor models

Determination of the fractional metabolism of ivacaftor by CYP3A4. For the PBPK model of ivacaftor, in the absence of an *in vitro* estimate, clinical interaction data with strong modulators of CYP3A4 were used to assign fmCYP3A4. First, we predicted the DDI with ketoconazole by varying the fmCYP3A4 value of ivacaftor from 95 to 100% (**Figure S1a**), since it has been reported that the fractional metabolism of ivacaftor assigned to CYP3A4 is greater than 95%.[15] An fmCYP3A4 of 98% predicted the AUC ratio (geometric mean ratio (GMR) 6.95) of ivacaftor within the bioequivalence limit (80–125%) of the observed AUC ratio (GMR 8.45). Repeating this analysis for rifampin indicated the magnitude of the DDI was well captured with fmCYP3A4 between 98% and 100% (simulated GMR 0.11 vs. observed 0.11) (**Figure S2b**). Taken together, the fmCYP3A4 value of 98% was chosen as it describes the observed DDIs between ivacaftor and ketoconazole or rifampin within the bioequivalence limit.

PBPK models of elexacaftor-tezacaftor-ivacaftor recapitulated clinically observed PK profiles. Model predictive performance of elexacaftor-tezacaftor-ivacaftor was assessed using observed pharmacokinetic data sets from clinical trials.[12,13] The observed and simulated plasma concentration-time profiles of elexacaftor-tezacaftor-ivacaftor following a single oral dose administration of elexacaftor 200 mg, tezacaftor 100 mg, and ivacaftor 100 mg in healthy participants are shown in **Figure S2**. For elexacaftor and tezacaftor, the mean plasma concentrations were used in the graph while the median plasma concentrations were used for ivacaftor as the median value that was reported from an ivacaftor single-dose PK study. The pharmacokinetic profile of elexacaftor-tezacaftor-ivacaftor after single oral dose administration was captured well by the PBPK model.

Further verification of the model was performed by simulating the steady-state PK of elexacaftor-tezacaftor-ivacaftor using the standard dosing regimen. The predicted steady-state AUC and C_{max} of elexacaftor-tezacaftor-ivacaftor were in the range of 0.9–1.2 of the observed values, demonstrating the excellent

Table 1 Comparison of PK parameters between simulated and observed data

PK study			Steady-state PK parameters			
			Simulated		Observed	
Drug	Regimen		C_{max} (mg/L)	AUC[a] (mg·hour/L)	C_{max} (mg/L)	AUC[a] (mg·hour/L)
Elexacaftor	200 mg q.d.	Mean	8.1	158.0	8.8	167.0
		CV (%)	40.0	45.7	24.6	30.2
		Simulated/observed	0.9	0.9	-	-
Tezacaftor	100 mg q.d.	Mean	8.3	114.0	6.7	92.4
		CV (%)	38.8	49.9	20.8	25.8
		Simulated/observed	1.2	1.2	-	-
Ivacaftor	150 mg q12h	Mean	1.6	13.4	1.3	12.1
		CV (%)	51.4	61.2	27.8	34.5
		Simulated/observed	1.2	1.1	-	-

Comparison of PK parameters between simulated and observed data for model verification of elexacaftor-tezacaftor-ivacaftor.
AUC, area under the curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; q.d., once daily; q12h, every 12 hours.
[a]$AUC_{(0-24h)}$ for elexacaftor and tezacaftor, and $AUC_{(0-12h)}$ for ivacaftor.

performance of the model. The observed and simulated PK parameters of elexacaftor-tezacaftor-ivacaftor are summarized in **Table 1**. In addition, the predicted mean AUC of M1-tezacaftor was 2.15-fold higher than that of the parent compound at the steady-state, which was close to what was previously observed (2.07-fold difference of metabolite and parent compound[12]).

PBPK-DDI models of elexacaftor-tezacaftor-ivacaftor recapitulated clinically observed drug interactions. Although preliminary PK simulations verified the predicted PK of elexacaftor-tezacaftor-ivacaftor, given that the PBPK models of elexacaftor-tezacaftor-ivacaftor are intended to be applied for the characterization of DDIs involving CYP3A modulation, it is essential to verify the victim properties defined in the models by simulating independent clinical DDI studies with a range of perpetrator drugs. The robustness of the model was assessed by comparing the magnitude of simulated DDIs of elexacaftor-tezacaftor-ivacaftor with that observed from the clinical trials. The PBPK-DDI models accurately recapitulated the observed DDI magnitude (**Table 2**).

DDI simulation of elexacaftor-tezacaftor-ivacaftor with ritonavir

Simulated DDI of elexacaftor-tezacaftor-ivacaftor and ritonavir suggests significant DDI. The verified PBPK-DDI models of elexacaftor-tezacaftor-ivacaftor were used to simulate the standard dose of elexacaftor-tezacaftor-ivacaftor when coadministered with nirmatrelvir-ritonavir to determine the magnitude of the DDI for its intended use for treatment of COVID-19. To mimic the clinical setting of nirmatrelvir-ritonavir administration, we simulated steady-state PK of elexacaftor-tezacaftor-ivacaftor, then ritonavir q12h for 5 days while continuing elexacaftor-tezacaftor-ivacaftor standard dosing during and after ritonavir administrations. We calculated the C_{max} and AUC ratio of elexacaftor-tezacaftor-ivacaftor in the presence and absence of ritonavir on Day 6 of coadministration (**Table S4**). The magnitude of DDI achieves its maximum level on Day 6, since elexacaftor-tezacaftor-ivacaftor has not achieved a new steady state after ritonavir administration (**Figure 2a–c**). In addition, the maximum CYP3A4 inhibition effect is maintained through Day 6 (**Figure 2e**). The simulated geometric mean AUC ratio was highest for ivacaftor (9.31, 90% confidence interval (CI): 8.28, 10.47), followed by tezacaftor (3.11, 90% CI: 2.96, 3.27) and elexacaftor (2.31, 90% CI: 2.20, 2.42).

Plasma concentrations of elexacaftor-tezacaftor-ivacaftor in the presence and absence of ritonavir is shown in **Figure 2**. Although ritonavir itself is eliminated the day after discontinuation (**Figure 2d**), the CYP3A4 inhibition is time dependent,[23] so the inhibition is prolonged and the recovery time to baseline is reliant on the turnover of the CYP3A4 itself (**Figure 2e**). Thus, baseline steady state of all elexacaftor-tezacaftor-ivacaftor drugs is predicted to be re-established on Day 15 with AUC ratios within 1.13–1.17 for all three components. Crucially, this indicates that dose adjustment of elexacaftor-tezacaftor-ivacaftor in the case of coadministration with nirmatrelvir-ritonavir would be required to extend beyond the 5 days of coadministration.

Altered dose of elexacaftor-tezacaftor-ivacaftor to recapitulate the PK profile of standard dose elexacaftor-tezacaftor-ivacaftor alone. We next utilized the models to simulate elexacaftor-tezacaftor-ivacaftor dose adjustments when these agents are coadministered with ritonavir and determine how long the adjusted dosage needed to be maintained, to overcome the enzyme inhibition effect mediated by ritonavir. Based on the simulated effects of ritonavir, elexacaftor 200 mg, tezacaftor 100 mg, ivacaftor 150 mg in the morning (two orange tablets) every 4 days (administered on Day 1 and Day 5 and resumed full dose on Day 9) provided a steady-state PK profile similar to the conventional regimen of elexacaftor-tezacaftor-ivacaftor alone (**Figure 3**). The trough

Table 2 Summary of the simulated vs. observed GMR of PK parameters

DDI study	PK parameters		Simulated GMR (90% CI)	Observed GMR (90% CI)	Ratio (simulated/observed)
Ivacaftor ± Ritonavir	C_{max} Ratio		2.61 (2.47, 2.77)	2.28 (1.84, 2.83)	1.14
	AUC Ratio		3.64 (3.37, 3.94)	3.06 (2.36, 3.97)	1.19
Ivacaftor ± Ketoconazole	C_{max} Ratio		2.04 (1.96, 2.12)	2.65 (2.21, 3.18)	0.77
	AUC Ratio		6.95 (6.44, 7.49)	8.45 (7.14, 10.01)	0.82
Ivacaftor ± Fluconazole	C_{max} Ratio		2.72 (2.64, 2.81)	2.47 (1.93, 3.17)	1.10
	AUC Ratio		3.33 (3.21, 3.46)	2.95 (2.27, 3.82)	1.13
Ivacaftor ± Rifampin	C_{max} Ratio		0.29 (0.27, 0.31)	0.20 (0.17, 0.24)	1.45
	AUC Ratio		0.11 (0.10, 0.13)	0.11 (0.10, 0.14)	1.00
Tezacaftor ± Itraconazole	Tezacaftor	C_{max} Ratio	2.62 (2.53, 2.72)	2.83 (2.62, 3.07)	0.93
		AUC Ratio	3.85 (3.65, 4.07)	4.02 (3.71, 4.63)	0.96
	M1-tezacaftor	C_{max} Ratio	0.59 (0.53, 0.65)	0.60 (0.54, 0.66)	0.98
		AUC Ratio	0.60 (0.54, 0.66)	0.60 (0.55, 0.66)	1.00
Elexacaftor ± Itraconazole	C_{max} Ratio		1.08 (1.08, 1.09)	1.05 (0.98, 1.13)	1.03
	AUC Ratio		2.00 (1.94, 2.06)	2.83 (2.59, 3.10)	0.71

Summary of the simulated vs. observed geometric mean ratio (GMR) of PK parameters in the presence and absence of CYP3A modulators.
AUC, area under the curve; CI, confidence interval; C_{max}, maximum plasma concentration; DDI, drug–drug interaction; PK, pharmacokinetic.

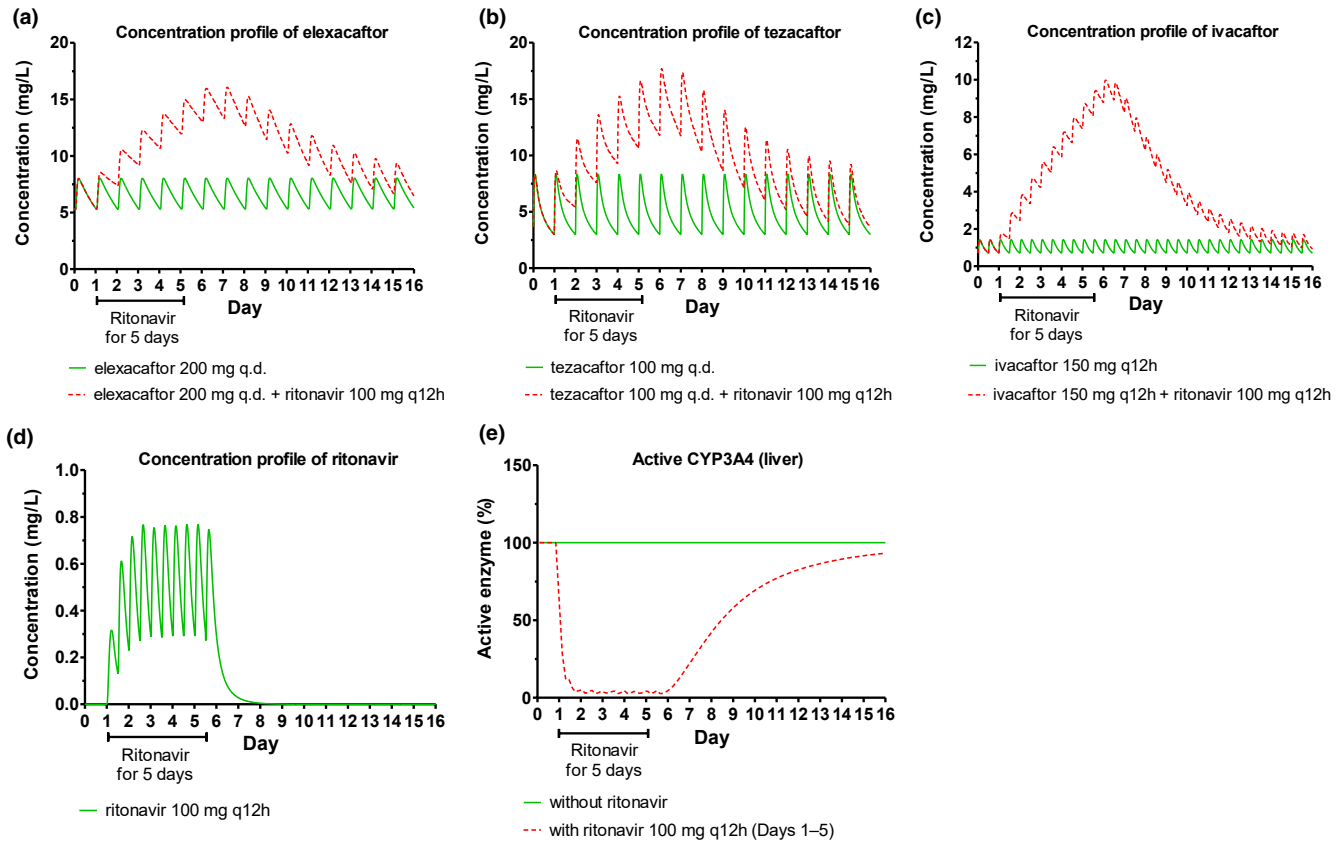

Figure 2 Plasma concentration profile of (**a**) elexacaftor, (**b**) tezacaftor, (**c**) ivacaftor, and (**d**) ritonavir, and (**e**) the percentage of active CYP3A4 enzyme over time. Green: without ritonavir; red: with ritonavir administered Day 1 through Day 5. CYP3A4, cytochrome P450 3A4; q.d., once daily; q12h, every 12 hours. [Colour figure can be viewed at wileyonlinelibrary.com]

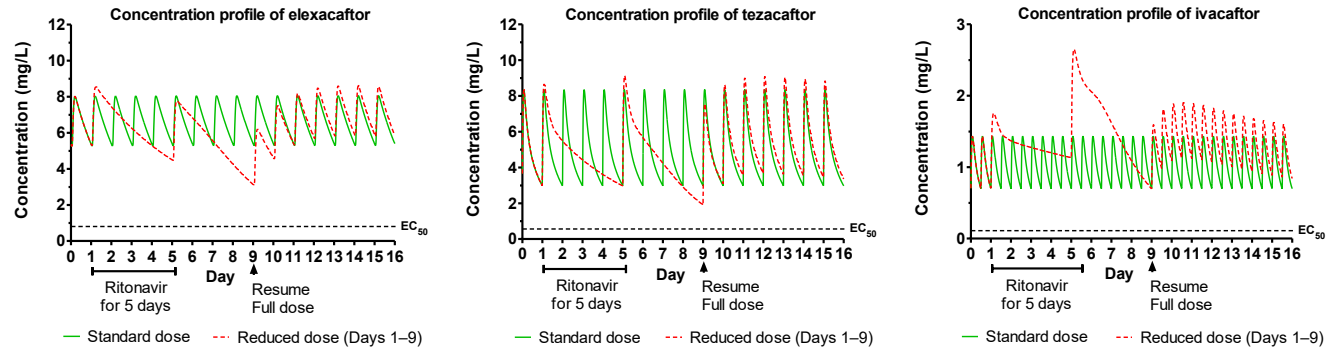

Figure 3 Plasma concentration profile of elexacaftor-tezacaftor-ivacaftor. Green: standard dose without ritonavir; red: reduced dose with ritonavir 150 mg q12h administered Day 1 through Day 5. (EC_{50} for tezacaftor and ivacaftor: obtained from exposure–response analysis in clinical trials regarding the reduction of sweat chloride; EC_{50} for elexacaftor: obtained from *in vitro* study of chloride transport in phe508del/phe508del human bronchial epithelial cells as no *in vivo* data are available.) EC_{50}, half maximal effective concentration; q12h, every 12 hours. [Colour figure can be viewed at wileyonlinelibrary.com]

concentrations of elexacaftor-tezacaftor-ivacaftor were all above the half maximal effective concentration (EC_{50}) targets, which are 0.99, 0.5, and 0.048 mg/L for elexacaftor, tezacaftor, and ivacaftor, respectively.[11–13] Since CYP3A4 inhibition dynamics mediated by ritonavir change over time, we measured the mean C_{max} and AUC of reduced dosing of elexacaftor-tezacaftor-ivacaftor regarding the first dose on Day 1 and the second dose on Day 5 and calculated the percentage of elexacaftor-tezacaftor-ivacaftor standard regimen alone (**Table 3**). The area under the curve from time zero to 96 hours ($AUC_{(0-96h)}$) of reduced dosing regimen ranged from 83.0% to 142.5% of elexacaftor-tezacaftor-ivacaftor alone. Resumption of the full dose of elexacaftor-tezacaftor-ivacaftor on Day 9 is based on simulations to optimize the concentration profiles of all components of elexacaftor-tezacaftor-ivacaftor, where

Table 3 Predicted mean C_{max} and AUC of reduced dose of elexacaftor-tezacaftor-ivacaftor

Drug regimen with ritonavir administered Days 1 through 5			C_{max} and % of standard dose elexacaftor-tezacaftor-ivacaftor alone		AUC and % of standard dose elexacaftor-tezacaftor-ivacaftor alone	
Drug	Regimen	Days	C_{max} (mg/L)	% of elexacaftor-tezacaftor-ivacaftor alone	AUC[a] (mg·hour/L)	% of elexacaftor-tezacaftor-ivacaftor alone
Elexacaftor	200 mg on Day 1	Days 1–2	8.7	107.4	185.9	117.7
		Days 1–5			605.3	95.8
	200 mg on Day 5	Days 5–6	7.9	97.5	168.9	106.9
		Days 5–9			524.4	83.0
Tezacaftor	100 mg on Day 1	Days 1–2	8.7	104.8	158.2	138.8
		Days 1–5			451.0	98.9
	100 mg on Day 5	Days 5–6	9.2	110.8	165.6	145.3
		Days 5–9			426.8	93.6
Ivacaftor	150 mg on Day 1	Days 1–2	1.8	112.5	35.9	134.0
		Days 1–5			125.2	116.8
	150 mg on Day 5	Days 5–6	2.7	168.8	54.4	203.0
		Days 5–9			152.8	142.5

Predicted mean C_{max} and AUC of reduced dose of elexacaftor-tezacaftor-ivacaftor (elexacaftor 200 mg–tezacaftor 100 mg–ivacaftor 150 mg q96h) with ritonavir 150 mg q12h administered Day 1 through Day 5.
AUC, area under the curve; C_{max}, maximum plasma concentration; q12h, every 12 hours.
[a]$AUC_{(0–24h)}$ for Days 1–2 and Days 5–6, $AUC_{(0–96h)}$ for Days 1–5 and Days 5–9.

the level of elexacaftor and tezacaftor do not become lower than 80% of the standard regimen before resuming the full dose, while striving to maintain levels of ivacaftor below 125% of the standard regimen after resuming the full dose. At Day 9, the CYP3A4 enzyme activities were recovered to 60% of the steady-state values.

In addition, we simulated an alternate dosing regimen, which is elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg in the morning (1 orange tablet) administered every 2 days. This regimen provided concentration profiles closer to the standard regimen of elexacaftor-tezacaftor-ivacaftor alone with less fluctuation between peak/trough concentrations (**Figure S3 and Table S5**). Especially for ivacaftor on Day 5 which showed higher C_{max} (2.7 mg/L, 168.8% of standard regimen) in the case of 150 mg q96h, the C_{max} of ivacaftor was 2.1 mg/L (131.3% of standard regimen) with the 75 mg q48h. However, the dosing regimen of two orange tablets every 3–4 days is consistent with recommendations for other strong CYP3A inhibitors and the C_{max} and AUC values between the two regimens were not demonstrably different.

For the dosing recommendation of tezacaftor/ivacaftor (Symdeko), since it is provided as a fixed dose yellow tablet consisting of tezacaftor 100 mg and ivacaftor 150 mg, the same dosing recommendation above (tezacaftor-ivacaftor 100–150 mg q96h) can be applied. Also, for the ivacaftor 150 mg tablet (Kalydeco), the same dosing recommendation (one tablet q96h) can be applied, but alternatively, the dosing interval of ivacaftor could be further increased to 5 days rather than 4 days, to recapitulate a PK profile similar to the standard regimen. When ivacaftor 150 mg was administered on Day 6 instead of Day 5, the $AUC_{(0–24h)}$ was decreased to 48.31 mg·hour/L (180.2% of standard regimen) from 54.4 mg·hour/L (203.0% of standard regimen) (**Table S6**). Taken together, the suggested dosing schedule of CFTR modulators co-administered with nirmatrelvir-ritonavir is described in **Figure 4**.

Discussion

All three components of elexacaftor-tezacaftor-ivacaftor are eliminated predominantly through hepatic metabolism along with limited renal excretion. The clinical DDI study with strong CYP3A4 inhibitors (ketoconazole and itraconazole) or inducer (rifampin) showed that elexacaftor-tezacaftor-ivacaftor are sensitive CYP3A4 substrates. Therefore, the safe and effective use of CFTR modulators is complicated by DDI management with concomitant CF medications, as CYP3A4 modulation by inducers or inhibitors can lead to altered systemic exposure, resulting in variability in drug response. Patients with CF often take multiple antibiotics, including rifamycins, macrolides, and azole antifungals, which potentially inhibit or induce CYP3A4-mediated metabolism of elexacaftor-tezacaftor-ivacaftor. Recently Tsai *et al.*[15] published an elexacaftor-tezacaftor-ivacaftor PBPK model to evaluate exposures during the transition from mono or dual combination of CFTR modulators to elexacaftor-tezacaftor-ivacaftor. We extended the models by refining the ivacaftor model and further validating the elexacaftor-tezacaftor-ivacaftor PBPK-DDI model with published clinical DDI data. Since the elexacaftor-tezacaftor-ivacaftor PBPK-DDI model we employed could robustly predict PK parameters and the observed drug interactions of elexacaftor-tezacaftor-ivacaftor, it can provide an approach to the evaluation and management of other potential DDIs involving CFTR modulators.

In particular, we aimed to provide guidance for elexacaftor-tezacaftor-ivacaftor dose adjustment with ritonavir, the CYP3A inhibitor and the component of nirmatrelvir-ritonavir for the treatment of COVID-19. From the elexacaftor-tezacaftor-ivacaftor-ritonavir DDI simulations, we found that when ritonavir 100 mg q12h was administered for 5 days, it led to the AUC ratio of ivacaftor of 9.31 (90% CI: 8.28, 10.47), which far

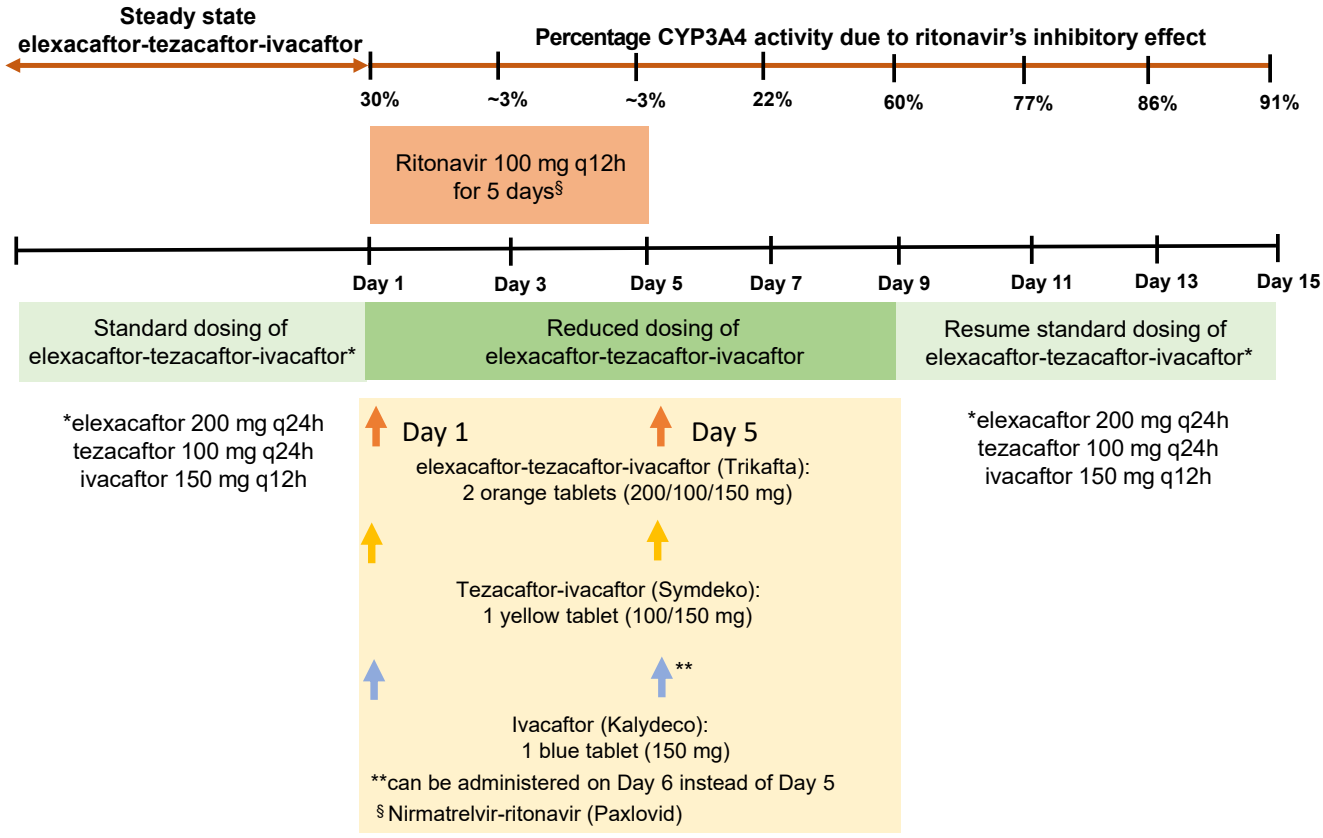

Figure 4 Suggested dosing schedule of CFTR modulators coadministered with nirmatrelvir-ritonavir. CFTR, cystic fibrosis transmembrane conductance regulator; CYP3A4, cytochrome P450 3A4; q12h, every 12 hours. [Colour figure can be viewed at wileyonlinelibrary.com]

exceeded the observed and simulated AUC ratio (3.64 and 3.06, respectively) when ivacaftor was administered with ritonavir 50 mg q24h.[21] The increase in interaction with the higher dose ritonavir shows that dose adjustments should not be estimated based on clinical data where the dosing of the inhibitor differs. Further, through the simulations we found that the elevated concentrations of elexacaftor-tezacaftor-ivacaftor were sustained for several days after ritonavir is eliminated due to irreversible inhibition of CYP3A4. The suggested reduced dosing regimen with resumption of full-dose elexacaftor-tezacaftor-ivacaftor 4 days after ritonavir discontinuation provided a PK profile similar to the standard regimen of elexacaftor-tezacaftor-ivacaftor alone.

The rationale for dose adjustment of elexacaftor-tezacaftor-ivacaftor is to avoid significant accumulation and risk for AEs. Results of the phase III trials showed an increased prevalence of elevations in hepatic transaminase and respiratory-related AEs in patients receiving elexacaftor-tezacaftor-ivacaftor when compared with placebo.[1,20] While early-phase clinical trials did not demonstrate any dose-related safety concerns, the degree of elevation in concentrations of ivacaftor with ritonavir is predicted to far exceed the exposure measured in clinical trials. In addition, *in vitro* data demonstrate elevated ivacaftor concentrations cause destabilization of corrected phe508del CFTR, dramatically increasing its turnover rate, which could increase the potential for respiratory-related AEs.[24–26]

One potential concern is that the altered dose of elexacaftor-tezacaftor-ivacaftor results in subtherapeutic exposure during the coadministration with ritonavir. There is a published case report of acute pulmonary exacerbation in a patient with CF who was prescribed rifampin (a potent CYP3A4 inducer) while receiving ivacaftor.[27] However, the trough concentrations of elexacaftor, tezacaftor, and ivacaftor (3.18, 1.95, and 0.69 mg/L, respectively) with the reduced dose in combination with ritonavir all exceed the EC_{50} targets (0.99, 0.5, and 0.048 mg/L, respectively), suggesting that the potential risk of reduced efficacy due to subtherapeutic concentrations is low.

A limitation of this study is that there are no clinically observed ritonavir-tezacaftor or ritonavir-elexacaftor DDI data to validate our predictions. However, the predictions of drug interactions with ritonavir were preceded by the thorough validation of the elexacaftor-tezacaftor-ivacaftor PBPK models with clinical DDI data with other strong CYP3A4 inhibitors. In the absence of clinical data, we used the PBPK modeling approach to provide timely guidance for treatment of COVID-19 with nirmatrelvir-ritonavir in people with CF receiving concomitant CFTR modulator therapy, bridging the gap with urgent need for the proper dosing guidelines.

Another limitation of the study is that population system parameters specific to the CF population were not incorporated into the modeling due to the absence of data. However, changes in demography reflecting the CF population were incorporated. Furthermore,

a prior study evaluating the hepatic clearance of drugs showed that CYP3A enzyme activity is unaffected in people with CF[28] and the current weight of evidence based on comparisons of elexacaftor-tezacaftor-ivacaftor PK in healthy volunteers compared with patients suggests they are comparable.[11–13] Previous studies indicate that differences in pharmacokinetics of drugs in CF is attributed to differences in body composition and plasma protein concentrations secondary to nutritional deficiencies.[29] However, the BMI of the population with CF has increased over the years with continued improvements in CF care, including highly effective CF modulators and nutritional support,[9] to the extent it is now similar to that of healthy volunteers.[10]

Lastly, we did not include models of all active metabolites of elexacaftor-tezacaftor-ivacaftor, as there was insufficient information to build the models for M23-elexacaftor and M1-ivacaftor. M23-elexacaftor has similar potency to the parent drug, but the exposure of this metabolite is significantly lower when compared with elexacaftor.[13] M1-ivacaftor has reduced potency by 6-fold compared with ivacaftor, but its exposure is 4.89-fold higher than the parent drug, so it may potentially affect overall efficacy. There is evidence that its plasma concentration is decreased by 35% in the presence of rifampin, indicating that M1-ivacaftor may also be metabolized by CYP3A4.[30] This suggests that the metabolism of M1-ivacaftor could be inhibited upon ritonavir coadministration increasing its exposure, placing the patient at increased risk of AEs. M1-tezacaftor is an important metabolite due to its similar potency to parent drug as well as its high metabolite to parent AUC ratio.[12] Using the PBPK model of M1-tezacaftor, we were able to determine that the reduced dose of elexacaftor-tezacaftor-ivacaftor provided a mean $AUC_{(0–96h)}$ for M1-tezacaftor during the coadministration period with ritonavir that was 80.9% of the standard regimen of elexacaftor-tezacaftor-ivacaftor alone. This indicates that the therapeutic efficacy of tezacaftor with the adjusted regimen may be slightly reduced due to the decreased exposure of its active metabolite.

In conclusion, using a PBPK modeling approach, we determined an adjusted dose of elexacaftor-tezacaftor-ivacaftor when administered concomitantly with nirmatrelvir-ritonavir that will likely decrease the impact of a drug interaction. The outcome of this study ensures the use of nirmatrelvir-ritonavir for the treatment of COVID-19 in people with CF while continuing to receive highly active CFTR modulators. In addition, this work provides tools to evaluate and potentially overcome clinically important DDIs involving highly active CFTR modulator therapy.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

L.M.A. is an employee of Certara UK Limited (Simcyp Division). All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

E.H. wrote the manuscript. E.H., L.M.A., and P.M.B. designed the research. E.H. performed the research. E.H., L.M.A., P.S.C., A.P.R., and P.M.B. analyzed the data.

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