RESEARCH ARTICLE

Evaluation of the Potential for Drug-Drug Interactions with Inhaled Itraconazole Using Physiologically Based Pharmacokinetic Modelling, Based on Phase 1 Clinical Data

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Abstract

Itraconazole is a potent inhibitor of cytochrome P450 3A4 (CYP3A4), associated with numerous drug-drug interactions (DDI). PUR1900, a dry powder formulation of itraconazole for oral inhalation, results in high lung and low systemic exposure. This project used physiologically based pharmacokinetic (PBPK) modeling to assess the DDI potential of inhaled PUR1900, using midazolam as a "victim drug." The basic and mechanistic static models evaluated the DDI potential of PUR1900, assuming 5 mg of midazolam coadministration at steady-state itraconazole exposure. Subsequently, Simcyp® PBPK simulation software and pharmacokinetic data from a Phase 1 clinical trial with PUR1900 (NCT03479411) were used to optimize an existing itraconazole PBPK model. The model was applied to investigate the potential for CYP3A4 DDI when 5 mg of midazolam is co-administered with inhaled PUR1900 at a steady state in a virtual healthy population at PUR1900 doses up to 40 mg per day. The basic static and mechanistic static models suggested a strong likelihood for DDI with inhaled PUR1900. The PBPK model was consistent with PUR1900 Phase 1 trial data. The geometric mean C_{max} and AUC ratios of midazolam at a maximum dose of 40 mg PUR1900 were 1.14 and 1.26, respectively, indicating a minimal likelihood of DDI with inhaled PUR1900. The low systemic exposure of itraconazole when administered as PUR1900 results in minimal to no CYP3A4 inhibition, reducing the concern of drug-drug interactions. As the risk of CYP3A4 DDI is predicted to be significantly lower when itraconazole is administered via oral inhalation as PUR1900, it is likely that PUR1900 can be safely used for the treatment of pulmonary fungal infections in patients taking pharmaceuticals currently contraindicated with oral itraconazole.

Keywords allergic bronchopulmonary aspergillosis · cystic fibrosis · drug-drug interactions · itraconazole · pharmacokinetics · physiologically based pharmacokinetics

Introduction

Itraconazole is a triazole fungicidal with a broad spectrum of activity. Its mechanism of action involves inhibition of the conversion of lanosterol to ergosterol, disrupting fungal cell membrane synthesis (1). The clinical use of oral itraconazole is limited by unpredictable and variable pharmacokinetics, poor tolerability (2), cardiac adverse effects (3, 4), and concerns related to drug-drug interactions (DDI) (5). The DDI potential of itraconazole is related to its activity as a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) isoenzyme (6, 7). The impact on the CPY3A4 pathway alters the metabolism and consequently the plasma concentrations of other drugs metabolized by this pathway (5). Co-administration of a long list of drugs and drug classes with itraconazole is currently contraindicated due to the potential for DDI. The package insert for itraconazole lists over 40 contraindicated drugs and another 256 drugs for which special precautions should be taken (8, 9).

Pulmatrix is developing PUR1900, a dry powder formulation of itraconazole for oral inhalation for the treatment of allergic bronchopulmonary aspergillosis (ABPA) in subjects with asthma and cystic fibrosis (CF). *Aspergillus (A.) fumigatus* can colonize or infect the airways of patients with asthma and CF and lead to a complex hypersensitivity

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reaction. ABPA has a prevalence of up to 15% in people with cystic fibrosis (10) and an estimated 1.5% of patients in the general population with asthma (11). Although there is no approved treatment for ABPA, oral itraconazole is commonly prescribed and has been shown to be efficacious (12–14). However, the major challenge of itraconazole use is that, because of its potent inhibition of CYP3A4, numerous drugs used in the treatment of exacerbations of asthma or maintenance therapies for CF cannot be used safely with oral itraconazole. In a phase 1 study (NCT03479411) with inhaled itraconazole (PUR1900), high and consistent lung exposure with substantially lower systemic itraconazole exposure was achieved following inhaled delivery relative to oral dosing (15). This limited systemic exposure may be beneficial for patients for whom oral itraconazole is contraindicated.

In order to determine the DDI potential of a maximum 40 mg dose of orally inhaled itraconazole, we used data from previously published systemic exposure following an inhaled dose of 35 mg itraconazole (15). Using these data, we applied a basic static model, a mechanistic static model, and a physiologically based pharmacokinetic (PBPK) model of itraconazole and OH-itraconazole, the primary metabolite of itraconazole, to evaluate the potential risk of PUR1900 as "perpetator" of CYP3A4 DDIs using midazolam as a "victim" drug.

Methods

This was an *in silico* study using pre-existing data, and no ethical committee approval was required. The methods and results of the PUR1900 Phase 1 clinical study used for static equation calculation and model development are summarized in Hava *et al.*(15).

Basic Static Model of Reversible Inhibition

The basic and mechanistic static equations have been described in the FDA guidance for *in vitro* drug interaction studies (16) For PUR1900, the ratio of the intrinsic clearance value of a probe substrate in the absence and in the presence of itraconazole (R_1) was calculated using the observed C_{max} of itraconazole and OH-itraconazole, respectively, after 14 days of 35 mg of PUR1900 QD (15).

Calculation of the ratio of the intrinsic clearance value of a probe substrate in the absence and in the presence of an inhibitor in the gut ($R_{1,gut}$) was required for PUR1900, as itraconazole and OH-itraconazole are inhibitors of CYP3A4. Equation input values are listed in Table I.

An $R_1 \geq 1.02$ or $R_{1,gut} \geq 11$ indicates that a clinically significant drug-drug interaction may exist and requires further investigation (16).

Table I Parameters used for the Calculation of the *R* Values for the Static Equations of Reversible Inhibition

Parameter	Value	Source
Itraconazole		
Molecular weight (g/mol)	705.6	Simcyp V19 Itraconazole File
f_u	0.016	Simcyp V19 Itraconazole File
R_B	0.58	Simcyp V19 Itraconazole File
$K_{i,u,ITZ}$ (µM)	0.0013	Simcyp V19 Itraconazole File
OH-itraconazole		
Molecular weight (g/mol)	721.7	Simcyp V19 OH-itraconazole File
f_u	0.016	Simcyp V19 OH-itraconazole File
R_B	0.58	Simcyp V19 OH-itraconazole File
$K_{i,u,ITZ}$ (µM)	0.0023	Simcyp V19 OH-itraconazole File
PUR1900		
Dose (mg)	35	Hava (15)
F_a	0.159	Hava (15)
$C_{max,ITZ}$ (µM)	0.0215	Hava (15) day 14 C_{max}, converted to µM from ng/mL
$C_{max,OH-ITZ}$ (µM)	0.0120	Simcyp V19 OH-itraconazole File day 14 C_{max}, converted to µM from ng/mL
Midazolam		
F_a	1	Simcyp V19 Midazolam File
F_g	0.58	Simcyp V19 Midazolam File
f_m	0.84	Simcyp V19 Midazolam File
Biological parameters		
Q_{en} (L/hr/70 kg)	19	FDA DDI Guidance 2020 (16)
Q_h (L/hr/70 kg)	97	FDA DDI Guidance 2020 (16)

Mechanistic Static Model of Reversible Inhibition

The area under the plasma concentration-time curve ratio (AUCR) for reversible inhibitors was calculated according to the FDA guidance for *in vitro* drug interaction studies (16).

As a worst-case scenario, it was assumed that all of the inhaled dose was swallowed and subsequently delivered to the gut.

A weak, moderate, or strong DDI is defined as a calculated AUCR (weak: ≥ 1.25-fold, but < 2.00-fold; moderate: ≥ 2.00-fold, but < 5.00-fold; strong: ≥ 5.00-fold) (16).

PBPK Modelling

Study Design and Setup

To achieve the modelling objectives, this step in the investigation consisted of two parts, model optimization and application. Some of the key factors relating to each step are indicated below. Model optimization and application were performed using Simcyp (2019, Version 19 Release 2, Certara, Sheffield, UK). Data assembly and plotting were performed using RStudio (Version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). The virtual North European Caucasian population (physiological parameters including liver volume and blood flows, enzyme abundances) within Simcyp was used for all simulations (17). Except for demographic data, all parameter values for the healthy volunteer (HV) population are the same as those used for the Caucasian population.

Model Optimization

To simulate the plasma concentration-time profiles of itraconazole and OH-itraconazole after the inhaled administration of 35 mg PUR1900 (QD for 14 days), the Simcyp V19 itraconazole oral solution PBPK model was adapted to include absorption of itraconazole through the lung as well as the gut. The model assumes first-order absorption from the lungs to the systemic circulation. The structural model is shown in Supplemental Figure A. The trial design used for the optimization of first-order inhalation parameters was based on the study described in Hava *et al.* (15) in which subjects received PUR1900 35 mg QD for 14 days. That study measured itraconazole and OH-itraconazole data as summarized in Supplemental Tables A and B.

For the PBPK model development, ten virtual trials of six subjects, aged 21 to 58 years (33.3% female), were generated to assess variability across groups. The population of the virtual trial was selected to match the clinical study subjects. A range of values was tested for the proportion of dose inhaled, the fraction of itraconazole absorbed from the lung ($F_{a,1}$), and the first-order rate constant of itraconazole absorption

from the lung ($k_{a,1}$). These parameters were optimized to best fit the observed plasma concentration-time profiles and PK parameters of itraconazole and OH-itraconazole after multiple dose administration of PUR1900 on study day 14, after 35 mg PUR1900 (QD for 14 days). Briefly, the proportion of dose inhaled and $F_{a,1}$ was optimized to match the itraconazole AUC_{0-24h} on study day 14. Then, $k_{a,1}$ was optimized to capture C_{max}. Once the simulated multiple dose and C_{max} were within 0.8 to 1.25 of the observed values, the absorption parameters were further optimized to best predict the OH-itraconazole concentration-time profiles. Intestinal absorption, distribution, and elimination parameters of itraconazole and OH-itraconazole were unchanged from the verified itraconazole and OH-itraconazole models, assuming itraconazole follows linear kinetics even at low doses. This model assumes no metabolism of itraconazole to OH-itraconazole in the lung.

The first-order inhalation parameters were manually optimized by comparing the simulated profiles of PUR1900 to observed data. The first-order inhalation parameters used to simulate the plasma concentration profile of PUR1900 are shown in Table II.

Model Application

The CYP3A4 inhibition potential of PUR1900 was predicted using a representative virtual healthy population consisting of ten virtual trials of ten healthy subjects (50% female), aged 20 to 50 years. The victim drug (midazolam) was administered as a single dose of 5 mg without administration of PUR1900, then again on day 14 of daily administration of PUR1900 35 mg. The virtual DDI trials were repeated with the same virtual trial design and study population, with 40 mg of PUR1900 administered daily for 14 days.

Results

Calculation of the R Value for the Basic Model of Reversible Inhibition

R_1 was calculated for PUR1900 using the observed maximum concentration of itraconazole and OH-itraconazole following multiple inhaled doses of PUR1900 (35 mg QD)

Table II Final Input Optimized Absorption Parameters of PUR1900

Parameter	PUR1900	Reference
Proportion of dose inhaled (%)	99.9	Manually optimized
$F_{a,1}$	0.265	Manually optimized
$k_{a,1}$ (1/hr)	0.028	Manually optimized
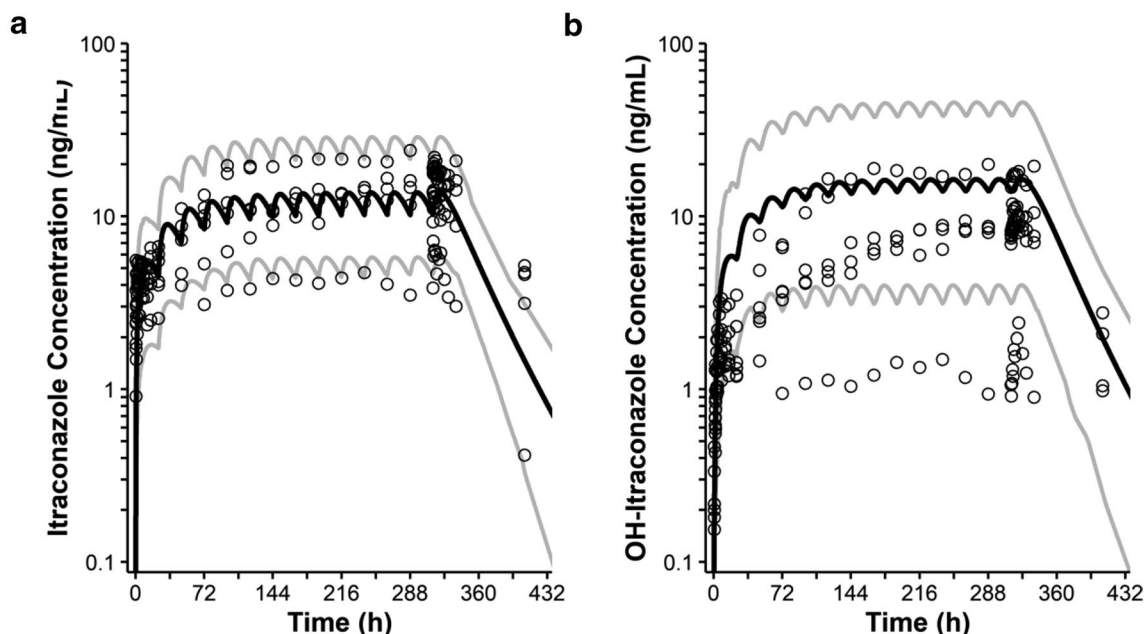
Fig. 1 Log-linear **a** itraconazole and **b** OH-itraconazole simulated and observed mean plasma concentration-time profiles after multiple oral dose of 35 mg QD PUR1900 for 14 days in healthy subjects. Depicted are sim- ulated (lines) and observed data (circles; mean of $n = 6$ individuals; Hava *et al.* 2020). The gray lines represent the 5th and 95th percentiles and the solid black line the mean data for the simulated population ($n = 60$)

for 14 days. R_1 was calculated to be 1.35. Because this value exceeded the cutoff value of 1.02 specified by the FDA guidance document (16), further investigation of DDI liability was required. Additionally, $R_{1,gut}$ was calculated to be greater than the threshold value of 11, indicating that additional assessment of DDI liability was required (16). Based on these results, a mechanistic static model was applied to further investigate the CYP3A4 inhibition potential of PUR1900.

Calculation of AUCR for the Mechanistic Static Equation

AUCR of midazolam was calculated for PUR1900 using the observed maximum concentration of itraconazole and OH-itraconazole following multiple simulated inhaled doses of PUR1900 (35 mg QD) for 14 days. To calculate the worst-case scenario, it was assumed that all itraconazole absorption occurred through the gut. The AUCR of midazolam was calculated to be 5.36, further indicating a risk of PUR1900 as a perpetrator of CYP3A4 DDIs. Based on these results, a PBPK model was developed to further understand the CYP3A4 inhibition potential of PUR1900.

PBPK Model Optimization and Application

Simulated itraconazole and OH-itraconazole plasma concentration data are based on the manually optimized proportion of dose inhaled, ($F_{a,1}$), and ($k_{a,1}$) parameters of PUR1900.

Individual mean trial concentrations and the mean concentration-time profiles for the total virtual population ($n = 60$) were simulated. The simulated profiles of PUR1900 and OH-itraconazole after 14 days of dosing with 35 mg/day of PUR1900 were comparable to the clinical data as shown in Fig. 1. In addition, the predicted geometric mean C_{max} and AUC_{0-24h} values for itraconazole on day 14 were within 0.81- and 0.96-fold, respectively, of the observed values (Table III). The predicted mean C_{max} and AUC_{0-24h} values

Table III Predicted and Observed Itraconazole Cmax and AUC_{0-24h} After Multiple 35 mg Inhaled Doses of PUR1900 (QD 14 Days)

	Day 1		Day 14	
	C_{max} (ng/mL)	AUC_{0-24h} (h·ng/mL)	C_{max} (ng/mL)	AUC_{0-24h} (h·ng/mL)
Simulated				
Geometric mean	4.93	97.4	12.3	266
CV%	49	48	51	53
5th percentile	1.81	35.6	28.8	627
95th percentile	9.74	197	28.8	627
Observed				
Mean	5.23	102	15.2	276
CV%	26	24	49	62
S/O	0.94	0.95	0.81	0.96

Table IV Predicted and Observed OH-itraconazole C_{max} and AUC$_{0-24h}$ After Multiple 35 mg Inhaled Doses of PUR1900 (QD 14 Days)

	Day 1		Day 14	
	C_{max} (ng/mL)	AUC_{0-24h} (h·ng/mL)	C_{max} (ng/mL)	AUC_{0-24h} (h·ng/mL)
Simulated				
Geometric mean	4.9	83.9	12.8	284
CV%	74	67	84	87
5th percentile	1.68	27.0	3.99	87.3
95th percentile	15.8	256	45.8	1025
Observed				
Mean	2.10	38.2	8.68	168
CV%	36	34	91	116
S/O	2.33	2.19	1.47	1.68

for OH-itraconazole on day 14 were within 1.47- and 1.68-fold, respectively, of the observed values (Table IV).

For model application, plasma concentration-time profiles of midazolam following a single oral dose of 5 mg in the absence of PUR1900 and on the 14th day of 14 days of dosing of PUR1900 (35 mg daily or 40 mg daily) to healthy subjects were simulated. The mean simulated plasma concentrations of itraconazole and OH-itraconazole after 14 days of 40 mg daily dosing of PUR1900 are presented in Fig. 2. Mean simulated plasma midazolam concentrations following a single oral dose of 5 mg in the absence of PUR1900 and on the 14th day of 14 days of dosing of PUR1900 (35 mg daily or 40 mg daily) to healthy subjects are shown in Fig. 3. The predicted geometric mean C_{max} and AUC_{0-inf} values and corresponding geometric mean ratios for midazolam in the presence and absence of PUR1900 are shown in Table V. The threshold for a weak DDI (AUCR and C_{max}R < 1.25) was not met when midazolam was coadministered with 35 mg daily of PUR1900. At the higher dose of 40 mg daily PUR1900, a weak DDI is predicted (AUCR ≥ 1.25 but < 2).

Discussion

Itraconazole is an effective treatment for ABPA in patients with asthma and CF (12, 13); however, the high risk of DDI when itraconazole is orally administered with CYP3A4 substrates limits its clinical use. Alternative formulations such as PUR1900, an inhaled formulation of itraconazole, allow for high exposure of itraconazole in the lungs, while minimizing the exposure in the gut and liver.

Previous studies have documented the systemic and pulmonary pharmacokinetics of oral itraconazole in adults and children (18). PUR1900 has been shown to achieve lung exposures that would be considered therapeutic for the treatment of pulmonary
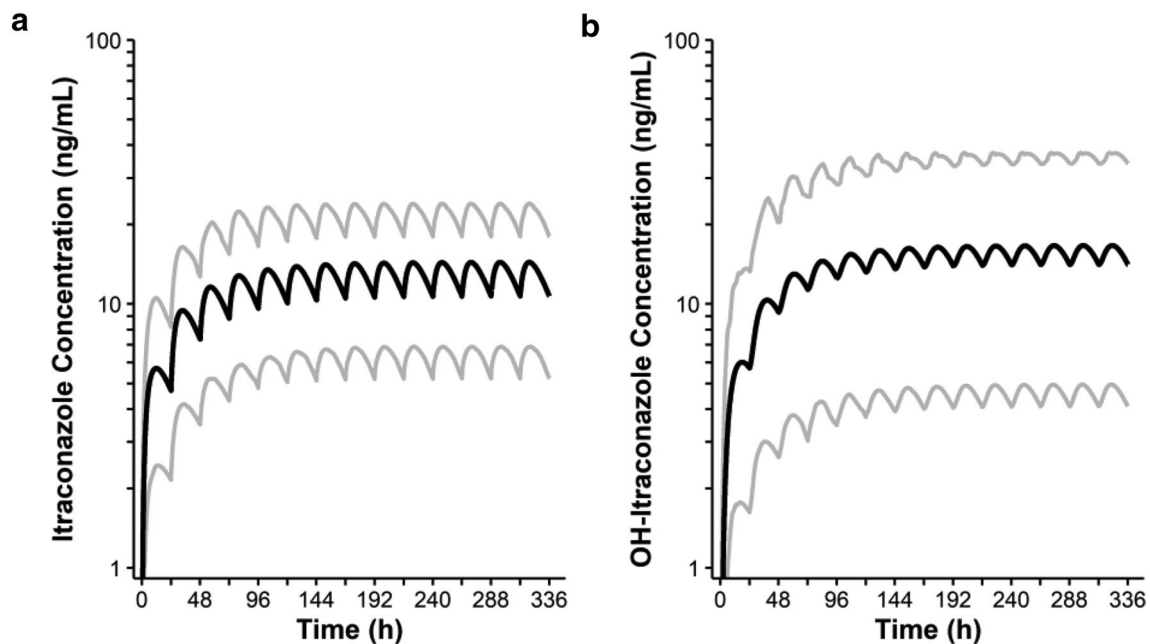
Fig. 2 Log-linear **a** itraconazole and **b** OH-itraconazole simulated mean plasma concentration-time profiles after multiple oral dose of 40 mg QD PUR1900 for 14 days in healthy subjects. Depicted are simulated (lines). The gray lines represent the 5th and 95th percentiles, and the solid black line the mean data for the simulated population (n = 100)
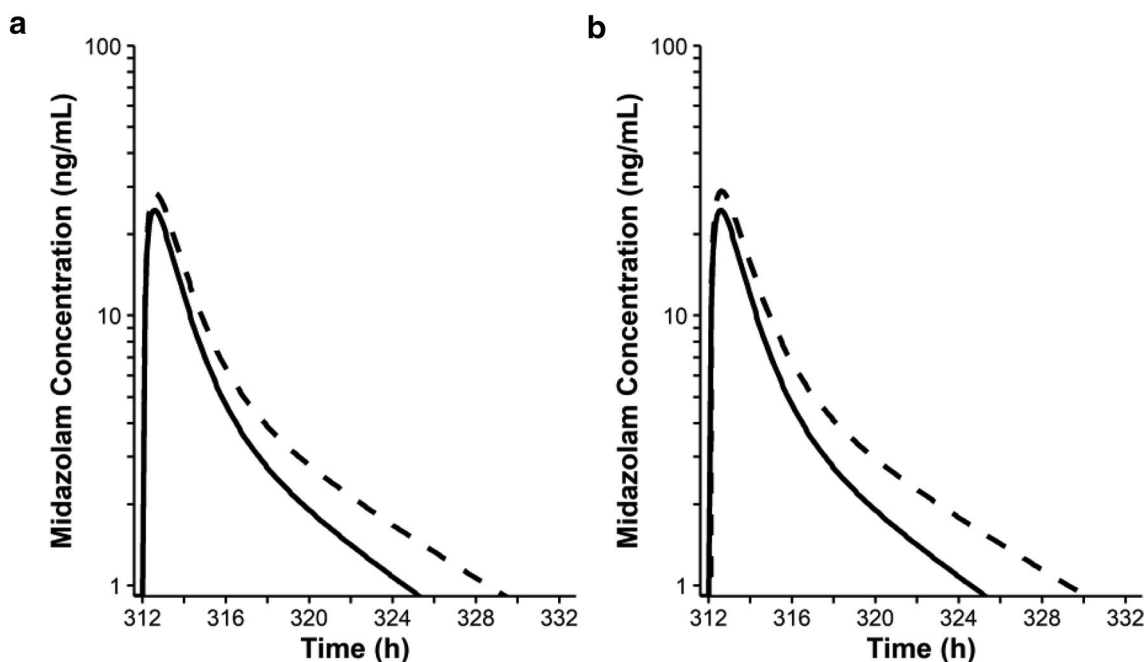
Fig. 3 Simulated log-linear plasma concentration-time profiles of a single 5 mg dose of midazolam, co-administered with steady state **a**) 35 mg and **b**) 40 mg of PUR1900 in healthy subjects. Depicted are simulated midazolam plasma concentration-time profiles in the absence of PUR1900 (solid line) and on the 14th day of 14 days of dosing of PUR1900 (dashed line). The lines represent the mean data for the simulated population ($n = 100$)

aspergillosis, after a single inhaled dose of 20 mg PUR1900 (15). While itraconazole is typically given with a corticosteroid, a study published in 2018 showed that itraconazole monotherapy is often effective in controlling acute ABPA (19). These studies demonstrate that itraconazole is an important tool in the treatment of ABPA.

Due to their extensive metabolism by CYP3A4, a number of CF-related treatments, including medications containing elexacaftor, ivacaftor, and tezacaftor (Trikafta®) (20), should not be used with oral itraconazole (21). Significant dosage adjustments are also recommended with other CFTR modulators such as Symdego®, Orkambi®, and Kalydeco®. Patients with CF are susceptible to numerous bacterial lung

infections as well, and certain antibiotics must be used with caution in the presence of itraconazole.

This study used static DDI models and PBPK models to evaluate the extent of CYP3A4 inhibition as a result of inhaled itraconazole via PUR1900. Static models showed a risk that PUR1900 may cause a DDI when coadministered with a sensitive CYP3A4 substrate such as midazolam. Static models for DDI assessment are limited as they do not account for time-dependent changes in drug concentration. Additionally, the assumption that all of the inhaled itraconazole is absorbed through the gut used in the mechanistic static model is conservative to account for a worst-case scenario. In contrast, PBPK models simulate the plasma

Table V Predicted Geometric Mean C_{max} and AUC_{0-inf} Values and Corresponding Geometric Mean Ratios for Midazolam in the Absence and Presence of PUR1900 (35 mg or 40mg QD for 14 Days) in Healthy Subjects

	Midazolam		Midazolam + PUR1900		GMR	
	AUC_{0-inf} (ng·hr/mL)	C_{max} (ng/mL)	AUC_{0-inf} (ng·hr/mL)	C_{max} (ng/mL)	AUC_{0-inf}	C_{max}
PUR1900 35 mg QD for 14 days						
Geometric mean	58.4	19.3	71.4	21.6	1.22	1.12
90% CI-lower	51.3	17.2	61.8	19.2	1.20	1.11
90% CI-upper	66.5	21.6	82.6	24.3	1.25	1.13
PUR1900 40 mg QD for 14 days						
Geometric mean	58.4	19.3	70.4	21.9	1.26	1.14
90% CI-lower	51.3	17.2	61.8	19.5	1.23	1.13
90% CI-upper	66.5	21.6	82.6	24.7	1.29	1.15

concentration-time profiles in virtual subjects and allow for absorption through both the gut and lungs (22).

Using PBPK techniques, we sought to evaluate the impact of inhaled itraconazole on the metabolism of midazolam. By adapting the existing oral PBPK model for itraconazole and OH-itraconazole within the Simcyp compound library, which have undergone robust verification with clinical DDI data, there is high confidence in the model predictions for PUR1900. Despite pharmacologic concentrations of itraconazole (the "perpetrator" drug) in the tissues of the lungs, there is minimal itraconazole exposure in the intestines and liver. As a result, there was minimal impact predicted on the metabolism of midazolam (the "victim" drug), despite the over-prediction of the primary active metabolite, OH-itraconazole.

The clinical implications of being able to administer itraconazole safely along with these disease-modifying drugs are clear. These results imply that itraconazole can be safely and effectively administered via an inhaled formulation even in patients taking one or more contraindicated drugs. This should improve the treatment possibilities for vulnerable patients maintained on medications that are contraindicated in the presence of oral itraconazole.

Limitations of this study are that this was an *in silico* simulation study, and such results must be verified *in vivo*. In addition, the subjects involved in the PBPK testing were otherwise healthy. However, the relative impact on CYP3A4 function should not be appreciably affected. Specifically, patients with ABPA should have a similar response of the cytochrome P450 system to itraconazole as healthy controls. In fact, Hava *et al.* (15) reported similar pharmacokinetics in patients with asthma compared to normal controls. Further testing is warranted with older and younger patients with underlying disease, particularly pulmonary disorders. Specific monitoring of blood levels of other victim drugs, including CFTR modulators, co-administered with PUR1900 would be helpful.

Conclusion

The minimal systemic exposure following orally inhaled itraconazole, dosed as PUR1900 dry powder formulation, results in less CYP3A4 inhibition. This is reflected in the weak interaction with midazolam. This can be extrapolated to other CYP3A4 substrates and reduces the concern of drug-drug interactions with PUR1900. It is likely that inhaled itraconazole can be safely used for the treatment of pulmonary fungal infections in patients concurrently treated with pharmaceuticals that are metabolized by CYP3A4.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1208/s12248-023-00828-z.

Declarations

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