Evaluation of drug–drug interaction potential for pemigatinib using physiologically based pharmacokinetic modeling

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Abstract
Pemigatinib is a potent inhibitor of fibroblast growth factor receptor being developed for oncology indications. It is primarily metabolized by cytochrome P450 (CYP) 3A4, and the ratio of estimated concentration over concentration required for 50% inhibition ratio for pemigatinib as an inhibitor of P-glycoprotein (P-gp), organic cation transporter-2 (OCT2), and multidrug and toxin extrusion protein-1 (MATE1) exceeds the cutoff values established in regulatory guidance. A Simcyp minimal physiologically based pharmacokinetic (PBPK) with advanced dissolution, absorption, and metabolism absorption model for pemigatinib was developed and validated using observed clinical pharmacokinetic (PK) data and itraconazole/rifampin drug–drug interaction (DDI) data. The model accurately predicted itraconazole DDI (approximate 90% area under the plasma drug concentration–time curve [AUC] and approximate 20% maximum plasma drug concentration [$C_{max}$] increase). The model underpredicted rifampin induction by 100% (approximate 6.7-fold decrease in AUC and approximate 2.6-fold decrease in $C_{max}$ in the DDI study), presumably reflecting non-CYP3A4 mechanisms being impacted. The verified PBPK model was then used to predict the effect of other CYP3A4 inhibitors/inducers on pemigatinib PK and pemigatinib as an inhibitor of P-gp or OCT2/MATE1 substrates. The worst-case scenario DDI simulation for pemigatinib as an inhibitor of P-gp or OCT2/MATE1 substrates showed only a modest DDI effect. The recommendation based on this simulation and clinical data is to reduce pemigatinib dose for coadministration with strong and moderate CYP3A4 inhibitors. No dose adjustment is required for weak CYP3A4 inhibitors. The coadministration of strong and moderate CYP3A4 inducers with pemigatinib should be avoided. PBPK modeling suggested no dose adjustment with P-gp or OCT2/MATE1 substrates.
INTRODUCTION

Pemigatinib is an inhibitor of the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases that is proposed for the treatment of malignant diseases or other diseases related to FGFR dysregulation. Pemigatinib has been approved by the US Food and Drug Administration, European Medicines Agency, and Japanese Ministry of Health, Labor, and Welfare and conditionally approved by Health Canada for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement.

Pemigatinib is a Biopharmaceutics Classification System Class II compound with high permeability and pH-dependent solubility. In vitro transport studies indicate that pemigatinib is a substrate of both P-glycoprotein (P-gp) and breast cancer resistance protein (data on file); however, the efflux mediated by P-gp and breast cancer resistance protein was saturated at concentrations of 1 and 30 μM, respectively, in vitro, suggesting that no drug–drug interactions (DDIs) are expected at clinically relevant exposures (e.g., for the recommended pemigatinib dose of 13.5 mg orally once daily [q.d.], geometric mean [coefficient of variation percent] steady-state [SS] AUC₀–₂₄h = 2620 nM · h [54%]; maximum plasma drug concentration \( C_{\text{max}} \) = 236 nM [56%]). Data from in vitro studies have indicated that cytochrome P450 (CYP) 3A4 is the major isozyme responsible for the metabolism of pemigatinib. In addition, pemigatinib is an inhibitor of P-gp, organic cation transporter-2 (OCT2), and multidrug and toxin extrusion protein-1 (MATE1).

Pemigatinib exhibited an approximately linear relationship for both \( C_{\text{max}} \) and area under the concentration–time curve (AUC) following oral dosing over the dose range studied in the first-in-human dose-escalation and cohort-expansion study conducted in patients with cancer (1–20 mg). Pemigatinib was rapidly absorbed with a terminal half-life of ~15 h. The recommended dose is 13.5 mg q.d. on a 2-weeks-on/1-week-off therapy schedule and 13.5 mg q.d. on a continuous schedule. At the 13.5-mg q.d. dose, the geometric mean SS \( C_{\text{max}} \) value was 236 nM, and the geometric mean area under the plasma concentration versus time curve at steady-state, over one dosing interval (AUCₜₘₙₙ₋ₐₜ) value was 2620 nM · h. Pemigatinib exhibited a low SS oral clearance with a geometric mean of 9.88–11.7 L/h and a moderate apparent volume of distribution with geometric mean of 173–244 L. The effect of food on pemigatinib plasma exposures in patients with cancer was modest and not clinically meaningful. In the fed state, median time taken to reach \( C_{\text{max}} \) was delayed to 4.0 h postdose. The
geometric mean of $C_{\text{max}}$ decreased by 18%, and the geometric mean of AUC over the dosing interval (tau) at SS ($\text{AUC}_{0-24}$) increased by 11%. A mass balance study showed that 12.6% and 82.4% of the total radioactivity was excreted in urine and feces of healthy participants, respectively (unpublished data). The oral absorption of pemigatinib was nearly complete, based on feces metabolite profiling. Renal excretion of pemigatinib was low (~1%), and liver metabolism is inferred to be the major clearance pathway for pemigatinib. A DDI study showed an approximate 90% increase in pemigatinib AUC with itraconazole coadministration and an 85% decrease in AUC with rifampin coadministration. The DDI study with acid-reducing agents showed that the geometric mean $C_{\text{max}}$ and AUC of pemigatinib decreased by 35% and 8%, respectively, upon coadministration with proton pump inhibitor, esomeprazole; the geometric mean $C_{\text{max}}$ and AUC of pemigatinib decreased by 2% and increased by 3%, respectively, upon coadministration with the histamine-2 antagonist ranitidine.

The ratio of intestinal luminal concentration estimated as dose in 250 ml/half = maximal inhibitory concentration (IC$_{50}$) for P-gp and unbound $C_{\text{max}}$/IC$_{50}$ for OCT2 and MATE1 is larger than 10, 0.1, and 0.02, respectively, and these values have exceeded the cutoff values proposed by the US Food and Drug Administration DDI guidance. Therefore, a physiologically based pharmacokinetic (PBPK) model was used to evaluate pemigatinib as an inhibitor of gut P-gp, OCT2, or MATE1.

The PBPK models that have been validated with observed clinical pharmacokinetic (PK) and DDI data can be used to predict the outcome for other DDI scenarios. The simulation results can also be used to support dose adjustment and label statements. The aim of this modeling and simulation study was to develop a PBPK model for pemigatinib using in silico, in vitro, and clinical data to predict the DDI.

**METHODS**

**Modeling strategy**

The Simcyp Population-Based Simulator Version 17 release 1 was used for all simulations (Simcyp). The physicochemical parameters of pemigatinib were measured by Incyte Corporation. The predictions of plasma drug concentration–time profiles and DDI for healthy volunteers and patients with cancer were performed in the Simcyp Simulator using the default Sim-Healthy Volunteer population and Sim-Cancer population, respectively.

The PBPK model for pemigatinib was built and verified using a mixed “bottom-up” and “top-down” approach using parameters from in silico calculation, in vitro experiments (“bottom-up”) and using in vivo clinical data (“top-down”) to bridge in vitro–in vivo translation. For research purposes, model workspace files are available at the following link: [https://members.simcyp.com/account/globalHealthRepository](https://members.simcyp.com/account/globalHealthRepository); model data set files are available as the following Supplementary Tables: Table S1 (Cohort 1 INCB054828 alone), Table S2 (Cohort 1 INCB05828 + itraconazole), Table S3 (Cohort 2 INCB054828 alone), and Table S4 (Cohort 2 INCB05828 + itraconazole).

**Pemigatinib PBPK model**

The initial PBPK model for pemigatinib was built using in vitro and in silico data. Data from in vitro studies have indicated that CYP3A4 is the major isozyme responsible for the metabolism of pemigatinib (data on file). Based on mass balance and metabolite identification, the oral absorption of pemigatinib is inferred to be nearly complete (1.4% of the administered radioactive dose was recovered as unchanged pemigatinib in feces), observed renal excretion is low (~1.0% of the dose was excreted in urine as unchanged pemigatinib), and liver metabolism is inferred to be the major clearance pathway for pemigatinib. Therefore, a minimal PBPK with advanced dissolution, absorption, and metabolism (ADAM) absorption model for pemigatinib that incorporates CYP3A4-mediated metabolism derived from in vitro data and human absorption, distribution, metabolism, and excretion (ADME) data was then further developed, and the model was used to describe the clinical PK data from pemigatinib-alone cohorts in the CYP3A4-mediated DDI study, and the PK data from the dose groups of 6–20mg in the phase I dose-escalation and dose-expansion study (NCT02393248). The sensitivity analysis of the pemigatinib fraction of drug metabolized by CYP3A4 ($f_{\text{CYP3A4}}$) on drug interaction with itraconazole (CYP3A4-mediated DDI study) suggested that CYP3A4 contributes ~55% of the metabolic clearance for pemigatinib. The verified pemigatinib model was then used to simulate the observed effect of itraconazole on pemigatinib PK and to confirm the contribution of CYP3A4 ($f_{\text{CYP3A4}} = 55\%$) to pemigatinib metabolic clearance.

**Application of pemigatinib PBPK model**

1. Prospective prediction of other strong, moderate, and weak CYP3A4 inhibitors or inducers: the final pemigatinib PBPK model was prospectively applied to estimate the effect of other strong, moderate, and weak CYP3A4 inhibitors or inducers. The simulation results were used for drug label and dose optimization in clinical trials.
2. Evaluation of pemigatinib as an inhibitor of gut P-gp, OCT2, or MATE1 substrates: a sensitivity analysis of pemigatinib P-gp inhibitor constant ($K_i$) value on the exposures of digoxin (a P-gp substrate) and a worst-case scenario simulation for the interaction between pemigatinib (20 mg q.d., highest dose evaluated in clinical trials, and assuming 10-fold lower measured in vitro $K_i$ values) and metformin (a OCT2/MATE1 substrate) were used to evaluate the effect of pemigatinib as an inhibitor of gut P-gp or OCT2/MATE1 substrates.

**Input data for pemigatinib PBPK model**

The parameters for the pemigatinib PBPK model are shown in Table 1. Simcyp default values are used for all other parameters in the model.

Pemigatinib is a diprotic base with pKa of 5.7 and 3.1, and the logP value for pemigatinib is 2.2. Pemigatinib primarily binds to albumin and the in vitro fraction of unbound pemigatinib in human plasma is 0.094. The measured blood/plasma value is 0.96, which is similar to the radioactivity blood/plasma value (0.80) determined in

| Table 1 | Summary of key input parameters for the pemigatinib physiologically based pharmacokinetic model |
|---------|--------------------------------------------------------------------------------------------------|
| Parameters | Value                                                                                       | Reference/data source                           |
| Molecular weight (g/mol) | 487.5                                                                                     | Experimental data                               |
| logP | 2.2                                                                                           | Experimental data                               |
| Compound type | Diprotic base                                                                               | Experimental data                               |
| $pK_a$ | 5.7, 3.1                                                                                     | Experimental data                               |
| B/P | 0.96                                                                                           | Experimental data                               |
| $f_u$ | 0.094                                                                                         | Experimental data                               |
| $P_{eff,caco-2}$ | $10^{-6}$ cm/s                                                                 | Experimental data                               |
| Reference $P_{eff,caco-2}$ | $10^{-6}$ cm/s (metoprolol)                                                               | Experimental data                               |
| Predicted $P_{eff,man}$ | $(x10^{-4}$ cm/s)                                                                            | Predicted from Caco-2 transport data after calibration |
| Solubility-pH profile | 0.71, 0.65, 0.20, 0.03, 0.001, and 0.001 mg/ml at pH 1.2, 2.0, 3.3, 4.3, 5.3, 6.5, and 7.4 | Experimental data                               |
| Precipitation model | Model 2                                                                                     | Optimized from clinical PK data for pemigatinib alone cohorts (CYP3A4-mediated DDI study) and adjusted $K_p$ scalar to match the PK data |
| $V_{ss}$ (L/kg) | 2.84 (method 2)                                                                              | Optimized from clinical PK data for pemigatinib alone cohort (CYP3A4-mediated DDI study) |
| $K_p$ scalar | 4.58                                                                                         | Optimized from clinical PK data for pemigatinib alone cohort (itraconazole DDI study) |
| $V_{sac}$ (L/kg) | 1.87                                                                                         | Optimized from clinical PK data for pemigatinib alone cohort (CYP3A4-mediated DDI study) |
| $Q_{sac}$ (L/h) | 44.0                                                                                         | Optimized from clinical PK data for pemigatinib alone cohort (itraconazole DDI study) |
| $CL_{int,CYP3A4}$ (μl/min/pmol) | 0.172                                                                                   | Calculated using Simcyp retrograde model to achieve $f_{int,CYP3A4}$ of 55% of total $CL_{int}$ (14.5 L/h for pemigatinib alone cohorts in itraconazole DDI study) |
| Additional $CL_{int}$-HLM (μl/min/mg protein) | 19.2                                                                                     | Calculated using Simcyp retrograde model, entered as HLM $CL_{int}$ under additional CL |
| $CL_R$ (L/h) | 0.2                                                                                           | Human mass balance study (unpublished data)     |
| $K_p$ P-gp (μM) | 4.8                                                                                           | Experimental data                               |
| $K_p$ OCT2 (μM) | 0.075                                                                                         | Experimental data                               |
| $K_p$ MATE1 (μM) | 1.1                                                                                           | Experimental data                               |

Abbreviations: B/P, blood/plasma ratio; $CL_{int}$, intrinsic metabolic clearance; $CL_{po}$, clearance observed for oral administration; CLR, renal clearance; CYP3A4, cytochrome P450 3A4; DDI, drug–drug interaction; $f_{int,CYP3A4}$, fraction of drug metabolized by CYP3A4; $f_u$, fraction unbound; HLM, human liver microsomes; $K_p$, inhibitor constant; $K_p$, ratio of concentration of compound in tissue to compound in plasma at steady state; MATE1, multidrug and toxin extrusion protein −1; OCT2, organic cation transporter −2; $P_{eff,caco-2}$, Caco-2 cell effective permeability; $P_{eff,man}$, effective human intestinal permeability; P-gp, P-glycoprotein; PK, pharmacokinetics; $Q_{sac}$, intercompartmental clearance of single-adjusted compartment; $V_{sac}$, volume of single-adjusted compartment; $V_{ss}$, volume of distribution at steady state.
a human ADME study. Pemigatinib exhibits a high apparent permeability value (11 × 10⁻⁶ cm/s) at 50 µM across the Caco-2 monolayer. A high fraction of intestinal absorption (Fa) value of 0.96 was predicted from the ADAM model. The predicted Fa is comparable with the Fa estimated (near complete absorption) from the human ADME data. The solubility of pemigatinib at 37°C is ~0.71 mg/ml in pH 1.2 buffer, 0.65 mg/ml in pH 2.0 buffer, <0.001 mg/ml in pH 6.5 buffer, and <0.001 mg/ml in pH 7.4 buffer. These solubility data were used in the ADAM model.

The minimal PBPK model was used to describe the PK profiles of pemigatinib and the volume of distribution at SS (Vss) was predicted by Method 2 in the PBPK model. The Vss value in the PBPK model was obtained using parameter estimation on the tissue to plasma partition coefficient (Kp) scalar to match the observed clinical PK data from the pemigatinib-alone cohorts in the CYP3A4-mediated DDI study. The Kp scalar of 4.58 was estimated to obtain Vss of 2.84 L/h to fit the PK profile. In addition, parameter estimation was used to obtain the volume of the single-adjusting compartment (1.87 L/kg) and inter-compartmental clearance of the single-adjusting compartment (44.0 L/h) by fitting the observed PK profile.

The in vitro studies and a human ADME study have indicated that CYP3A4 is the major isozyme responsible for the metabolism of pemigatinib. The renal clearance of pemigatinib is ~0.2 L/h. Hepatic clearance through the CYP3A4 enzyme, CYP3A4 intrinsic clearance (CLint: 0.172 µl/min/pmoll), was estimated using the Simcyp retrograde calculator based on CLpo observed in the pemigatinib-alone cohort of the itraconazole DDI study (14.5 L/h) and predicted Fa (0.96) and predicted fraction of drug entering enterocytes and escaping the first-pass gut wall metabolism (Fa/fe: 0.93) when fM,CYP3A4 was assigned as 55%. The fM,CYP3A4 value in the PBPK model was confirmed by matching predicted pemigatinib PK profiles when administered concomitantly with itraconazole to the clinical observed data from the CYP3A4-mediated DDI study. Patients with cancer in the phase I dose-escalation and dose-expansion study showed similar CLpo (12.0 L/h) as healthy volunteers.

The bidirectional transport ratio of digoxin decreased in the presence of pemigatinib in a concentration-dependent manner with IC₅₀ of 4.8 µM. Pemigatinib inhibited the OCT2 and MATE1 with estimated IC₅₀ of 0.075 and 1.1 µM, respectively.

Simulations

All of the simulations were conducted using a 10 × 10 design (10 trials with 10 participants per trial) to simulate population variability. Visual checks of the predicted concentration–time profiles were performed, and the key PK parameters (AUC and Cmax) were compared. The model was considered to be acceptable when the ratio of the predicted observed parameter was not outside the range of 0.5- to 2-fold.

PBPK model development and validation

The pemigatinib PBPK model was validated by simulations of DDIs between pemigatinib and itraconazole or rifampin using a Simcyp virtual healthy volunteer population, with the study design matching the corresponding clinical DDI study in healthy volunteers. The itraconazole capsule (200 mg) was administered daily from Day 1 to Day 11, and a single 4.5-mg dose of a pemigatinib tablet was administered orally with itraconazole on Day 5. The rifampin capsule (600 mg) was administered daily from Day 1 to Day 12, and a single 13.5-mg dose of a pemigatinib tablet was administered orally with rifampin on Day 8. The simulations were performed using an age range of 18–55 years (proportion of female volunteers: 0.5), matching the demographics of the clinical DDI study in healthy volunteers (Cohort 1 [itraconazole]: median age, 34.5 years [range, 24–50 years]; male, 56%; White, 83%; mean body mass index [BMI], 26.8 kg/m² [SD, 3.09]; Cohort 2 [rifampin]: median age, 30 years [range, 19–49 years]; male, 39%; White, 72%; BMI, 26.4 kg/m² [SD, 3.99]). In addition, the pemigatinib PBPK model was further validated by simulation of pemigatinib PK at 6, 9, 13.5, and 20 mg q.d. doses using the Simcyp virtual cancer population, with the study design matching the corresponding phase I study in adults with advanced malignancies. The simulations were performed using an age range of 21–79 years (proportion of female volunteers: 0.5), matching the demographics of the phase I study (median age, 59.0 years [range, 21.0–83.0 years]; male, 39.1%; White, 89.1%; median BMI, 27.1 kg/m² [range, 17.6–49.0 kg/m²]).

Model application

Prospective prediction of other strong, moderate, and weak CYP3A4 inhibitors or inducers

The verified pemigatinib PBPK model was used to predict the effect of other strong (clarithromycin), moderate (diltiazem, erythromycin, and cyclosporine), and weak (fluvoxamine) CYP3A4 inhibitors and moderate (efavirenz) CYP3A4 inducers on pemigatinib PK. The Simcyp default PBPK models for clarithromycin, erythromycin, diltiazem, cyclosporine, fluvoxamine, and efavirenz were used in these simulations. For CYP3A4-mediated inhibition/
induction simulation, the inhibitors/inducers were administered daily from Day 1 to Day 12 and a single 13.5-mg dose of a pemigatinib tablet was administered orally on Day 8. The simulations were performed using an age range of 18–55 years (proportion of female volunteers: 0.5).

Prediction of the effect of pemigatinib on the PK of P-gp or OCT2/MATE1 substrates

The Simcyp built-in PBPK models of digoxin or metformin were used to evaluate P-gp– or OCT2/MATE1-mediated DDI for pemigatinib as inhibitor. In the simulation, pemigatinib was administered daily from Day 1 to Day 9, and a single dose of digoxin or metformin was administered orally with pemigatinib on Day 4. These simulations were performed with an age range of 18–55 years (proportion of female volunteers: 0.5).

RESULTS

PBPK model development

Simulation of pemigatinib PK

The observed and simulated mean plasma concentration–time profiles for pemigatinib following a single oral dose of pemigatinib alone in healthy volunteers (CYP3A4-mediated DDI study of pemigatinib alone) and patients with cancer (phase I dose-escalation and dose-expansion study) are shown in Figure 1. Predicted and observed geometric mean plasma C\text{max} and AUC values for pemigatinib tablets are shown in Table 2. For healthy volunteers, the simulated profiles of pemigatinib are very similar to the clinical data, and the predicted geometric mean C\text{max} and AUC\text{0–}\infty values are within 0.93- to 1.11-fold of the observed data. For patients with cancer, the simulated PK profiles of pemigatinib are comparable with the clinical data, and the predicted geometric mean C\text{max} and AUC values are within 0.61- to 1.17-fold of the observed data.

Simulation of DDI between pemigatinib and itraconazole or rifampin

The sensitivity analysis of pemigatinib f_{\text{mCYP3A4}} on drug interaction with itraconazole was used to determine the CYP3A4 contribution to the metabolic clearance of pemigatinib. The input of CYP3A4 CL_{\text{int}} was varied to obtain a range of f_{\text{mCYP3A4}} from 0.25 to 0.95 (using the Simcyp retrograde calculator). The simulations of itraconazole–pemigatinib DDIs with different f_{\text{mCYP3A4}} values for pemigatinib were compared with the observed DDI data. When f_{\text{mCYP3A4}} was assigned to be 55%, the best prediction was achieved by the PBPK model for the effect of DDI between pemigatinib and itraconazole. Ratios of predicted and observed values of C\text{max} and AUC in the presence or absence of itraconazole or rifampin are presented in Table 3. Simulated and observed plasma concentration–time profiles in the presence and absence of itraconazole or rifampin are presented in Figure 2. These data have been reported previously in the European Medicines Agency Public Assessment Report for pemigatinib. For itraconazole DDI, the pemigatinib AUC and C\text{max} ratios predicted by the model are similar to the observed values (Table 3); the predicted geometric mean AUC ratios and C\text{max} ratios are within the 90% confidence interval (CI) for the observed values. However, for rifampin DDI, AUC and C\text{max} values were underpredicted, with model-predicted pemigatinib AUC and C\text{max} ratios ~1.5- to 2-fold higher compared with the observed ratios.

PBPK model application

Simulation of pemigatinib DDI with various CYP3A4 inhibitors/inducers

The final pemigatinib PBPK model predicted the DDI from CYP3A4 inhibition well but was not able to accurately predict DDI between pemigatinib and rifampin. This could be attributed to an additional DDI effect on absorption of pemigatinib such as rifampin induction of intestinal P-gp and then decreasing of plasma concentrations of pemigatinib. The model with 55% f_{\text{mCYP3A4}} was used to predict the DDI effect on pemigatinib PK when coadministered with moderate and weak CYP3A4 inducers. Results of the simulated effects of strong, moderate, and weak CYP3A4 inhibitors/inducers on pemigatinib PK are summarized in Table 4 and illustrated in Figure 3.

The model-simulated pemigatinib geometric mean C\text{max} and AUC ratios, respectively, for coadministration were as follows: strong inhibitor clarithromycin (1.20 and 1.89); moderate inhibitors fluconazole (1.15 and 1.83), erythromycin (1.16 and 1.66), and diltiazem (1.13 and 1.51); weak inhibitor fluvoxamine (1.05 and 1.08); and moderate inducer efavirenz (0.76 and 0.48).

Simulation of pemigatinib DDI as gut P-gp or OCT2/MATE1 inhibitors

Digoxin and metformin were used as substrates of gut P-gp and OCT2/MATE1, respectively, to evaluate the DDI for pemigatinib as a gut P-gp or OCT2/MATE1 inhibitor.
To confirm the Simcyp built-in PBPK model for digoxin or metformin as substrate of P-gp or OCT2/MATE1, DDI simulations between digoxin and ritonavir (Simcyp built-in model) and metformin and cimetidine (Simcyp built-in model) were performed, and simulated DDI results were compared with clinical observation.12,13 Digoxin and ritonavir DDI simulation produced $C_{\text{max}}$ and AUC ratios of 1.39 and 1.26 for digoxin, and metformin and cimetidine DDI simulation produced $C_{\text{max}}$ and AUC ratios of 1.39 and 1.26 for digoxin, and metformin and cimetidine DDI simulation produced $C_{\text{max}}$ and AUC ratios of 1.51 and 1.55 for metformin. The simulated DDI effects are
The OCT2/MATE1-mediated DDI effect between metformin and pemigatinib was evaluated using PBPK modeling with coadministration of metformin 400 mg and pemigatinib 13.5 mg q.d. or 20 mg q.d. The simulated geometric mean ratios of $C_{\text{max}}$ and AUC were 1.041 and 1.046 when coadministered with 13.5 mg q.d. of pemigatinib and 1.054 and 1.061 when coadministered with 20 mg q.d. of pemigatinib. A worst-case scenario simulation was performed using 10-fold lower measured $K_i$ values ($K_{i,\text{OCT2}} = 0.0075 \mu M$ and $K_{i,MATE1} = 0.11 \mu M$) and coadministered with pemigatinib 20 mg q.d., and simulations showed $C_{\text{max}}$ and AUC geometric mean ratios of 1.29 and 1.41, respectively.

**DISCUSSION**

The PK profile of pemigatinib demonstrates an approximately linear exposure to dose relationship up to 20 mg,
the highest dose studied. Pemigatinib is eliminated predominantly through hepatic metabolism, whereas the contribution from renal excretion is minimal. The in vitro data suggest that the CYP3A4 plays a primary role in the metabolic clearance of pemigatinib. A clinical DDI study\(^7\) with itraconazole and rifampin confirmed that pemigatinib is a CYP3A4 substrate (AUC ratios of 1.88 and 0.149, respectively).

The PBPK model for pemigatinib was initially built using in vitro and physicochemical data. Then a minimal PBPK with an ADAM absorption model for pemigatinib that incorporates CYP3A4-mediated metabolism derived from in vitro data, mass balance data, and clinical PK data was developed. The pemigatinib PBPK model-predicted PK profiles describe the clinical data in healthy volunteers appropriately. Furthermore, the PBPK model-predicted PK profiles in patients with cancer describe the clinical data well. The contribution of CYP3A4 to the metabolic clearance \(f_{m\text{CYP3A4}}\) was first estimated by a sensitivity analysis of pemigatinib \(f_{m\text{CYP3A4}}\) on drug interaction with itraconazole, and it was further confirmed to be 0.55 by matching the simulated PK profiles of pemigatinib with or without coadministration of itraconazole to clinical DDI data. The metabolism and elimination of pemigatinib have been extensively evaluated in the human ADME study as well as a battery of in vitro studies. As noted in our previous work,\(^{14}\) in the human ADME study (unpublished data), 72% of the total radioactivity was accounted for by known metabolites; 76.9% of the metabolite burden in urine and feces was derived from M2 (O-desmethyl-pemigatinib) and its secondary metabolites. In vitro metabolism studies show that CYP3A4 is solely responsible for M2 formation from pemigatinib. Therefore, it is unlikely that there is yet another metabolic pathway that is responsible for >25% of total clearance of pemigatinib. The predicted geometric mean AUC ratio and \(C_{\text{max}}\) ratio

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**TABLE 4** Simulated pemigatinib drug–drug interactions with various CYP3A4 inhibitors or inducers

| CYP3A4 perpetrators and dose regimen | Inhibition/induction mechanism | AUC ratio, geometric mean (90% confidence interval) | \(C_{\text{max}}\) ratio, geometric mean (90% confidence intervals) |
|--------------------------------------|--------------------------------|-----------------------------------------------|-----------------------------------------------|
| Itraconazole 200 mg q.d.             | Strong, reversible inhibition | 1.98 (1.91–2.05)                               | 1.22 (1.20–1.24)                               |
| Clarithromycin 500 mg b.i.d.         | Strong, time-dependent inhibition | 1.89 (1.80–1.98)                              | 1.20 (1.18–1.21)                              |
| Fluconazole 400 mg q.d.              | Moderate, reversible inhibition | 1.83 (1.78–1.90)                              | 1.15 (1.13–1.16)                              |
| Erythromycin 500 mg b.i.d.           | Moderate, time-dependent inhibition | 1.66 (1.59–1.73)                            | 1.16 (1.14–1.17)                              |
| Diltiazem 60 mg t.i.d.               | Moderate, time-dependent inhibition | 1.51 (1.46–1.56)                            | 1.13 (1.12–1.14)                              |
| Fluvoxamine 50 mg q.d.              | Weak, reversible inhibition    | 1.08 (1.08–1.09)                              | 1.05 (1.04–1.05)                              |
| Rifampin 600 mg q.d.                 | Strong inducer                 | 0.323 (0.299–0.349)                           | 0.604 (0.572–0.638)                           |
| Efavirenz 600 mg q.d.                | Moderate inducer               | 0.482 (0.455–0.512)                           | 0.758 (0.736–0.781)                           |

**Note:** Values are presented in the format of geometric mean (90% confidence intervals).

Abbreviations: AUC, area under the plasma drug concentration–time curve; b.i.d., twice daily; \(C_{\text{max}}\), maximum plasma drug concentration; CYP3A4, cytochrome P450 3A4; q.d., once daily; t.i.d., three times daily.
EVALUATING PEMIGATINIB DDI USING PBPK MODELING

are within the 90% CI of the observed data for itraconazole DDI. However, underprediction is observed for rifampin DDI, and the model-predicted pemigatinib AUC and C(max) ratios are ~1.5- to 2-fold higher compared with the observed AUC and C(max) ratios for rifampin DDI. In the CYP3A4-mediated DDI study, an 85% reduction in AUC and 63% decrease in half-life of pemigatinib were observed following rifampin coadministration. In addition, the first-pass gut and liver metabolism is expected to be low as simulated in this PBPK model because of the high permeability and low oral clearance of pemigatinib. All of these suggest that a decrease in bioavailability of pemigatinib occurred with rifampin coadministration. However, a limitation to this study is that the final pemigatinib PBPK model was not able to accurately predict DDI between pemigatinib and rifampin, which could be attributed to additional DDI effects on the absorption of pemigatinib; the complexity associated with the disposition of rifampin and subsequent impact of those factors on DDI with rifampin are acknowledged in the literature. As such, it would be appropriate to identify other prototypical CYP34A inducers in place of rifampin in the future.

The worst-case scenario DDI simulation for pemigatinib and a weak CYP3A4 inhibitor. However, a limitation to this study is that the final pemigatinib PBPK model was not able to accurately predict DDI between pemigatinib and rifampin, which could be attributed to additional DDI effects on the absorption of pemigatinib; the complexity associated with the disposition of rifampin and subsequent impact of those factors on DDI with rifampin are acknowledged in the literature. As such, it would be appropriate to identify other prototypical CYP34A inducers in place of rifampin in the future.

The model with 55% f(mCYP3A4) predicted a >50% AUC decrease for coadministration with either strong or moderate CYP3A4 inducers. Therefore, coadministration of strong or moderate CYP3A4 inducers should be avoided. In addition, itraconazole increased pemigatinib exposure by about 90%, suggesting that pemigatinib is not a sensitive substrate. Therefore, the effect of a weak CYP3A4 inducer (such as dexamethasone) on pemigatinib is expected to be small.

The worst-case scenario DDI simulation for pemigatinib as an inhibitor of P-gp or OCT2/MATE1 substrates using 10-fold lower measured K_i values showed a modest DDI effect (1.25-fold C(max) and 1.41-fold AUC increase for digoxin and metformin, respectively), suggesting no dose adjustment for pemigatinib when coadministered with P-gp or OCT2/MATE1 substrates.

FIGURE 3 Observed and simulated AUC and C(max) ratios of a single dose of 13.5 mg pemigatinib with various cytochrome P450 3A4 inhibitors and inducers. AUC, area under the plasma drug concentration–time curve; C(max), maximum plasma drug concentration; CI, confidence interval; DDI, drug–drug interaction.
CONCLUSIONS

The PBPK modeling and simulation predicted itraconazole DDI appropriately, but could not recover the rifampin DDI data. The validated pemigatinib PBPK model was used to evaluate other CYP3A4 inhibitors/inducers to support the label and provide dose recommendations for clinical trials. The simulation results indicate that coadministration with strong or moderate CYP3A4 inhibitors should be avoided, which supports the approved label for pemigatinib; if unavoidable, the dose should be reduced from 13.5 to 9 mg or from 9 to 4.5 mg. No dose adjustment is required for coadministration of pemigatinib with weak CYP3A4 inducers. Therefore, coadministration of strong or moderate CYP3A4 inducers should be avoided, which supports the approved label for pemigatinib. The evaluation of pemigatinib as a P-gp or OCT2/MATE1 inhibitor using the pemigatinib PBPK model suggests that pemigatinib can be coadministered with P-gp or OCT2/MATE1 substrates without any dose adjustment.

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CONFLICT OF INTEREST

Tao Ji is a former employee and shareholder of Incyte Corporation. Xuejun Chen and Swamy Yeleswaram are employees and shareholders of Incyte Corporation.

AUTHOR CONTRIBUTIONS

T.J. wrote the manuscript. T.J., X.C., and S.Y. designed the research, performed the research, and analyzed the data.

REFERENCES

1. Liu PCC, Koblish H, Wu L, et al. INCB054828 (pemigatinib), a potent and selective inhibitor of fibroblast growth factor receptors 1, 2, and 3, displays activity against genetically defined tumor models. PLoS One. 2020;15:e0231877. doi:10.1371/journal.pone.0231877
2. PEMAZYRE™ (pemigatinib) tablets [prescription information]. Incyte Corporation; 2021.
3. Pemazyre (Pemigatinib) [Product Information]. Incyte Biosciences Distribution B.V.; 2021.
4. Pemazyre (ペマジール) (ペミガチニブ) tablets; Package Insert. Incyte Corporation; 2021.
5. Incyte Announces Health Canada Conditional Approval of Pemazyre (pemigatinib) as First Targeted Treatment for Adults with Previously Treated, Unresectable Locally Advanced or Metastatic Cholangiocarcinoma. Incyte Corporation; 2021.
6. Subbiah V, Iannotti NO, Gutierrez M, et al. FIGHT-101, a first-in-human study of potent and selective FGFR 1-3 inhibitor pemigatinib in pan-cancer patients with FGFR/FGFR alterations and advanced malignancies. Ann Oncol. 2022;33:522-533. doi:10.1016/j.annonc.2022.02.001
7. Ji T, Rockich K, Epstein N, et al. Evaluation of drug–drug interactions of pemigatinib in healthy participants. Eur J Clin Pharmacol. 2021;77:1887-1897. doi:10.1007/s00228-021-03184-z
8. US Food and Drug Administration. Guidance for industry: in vitro drug interaction studies — cytochrome p450 enzyme- and transporter-mediated drug interactions. 2020.
9. Ji T, Liouh C, Asatiani E, et al. Pharmacokinetics and pharmacodynamics of pemigatinib, a potent and selective inhibitor of FGFR 1, 2, and 3, in patients with advanced malignancies. Mol Cancer Ther. 2019;18(12 Suppl):C071. doi:10.1158/1535-7163.TARG-19-C071
10. Zhou W, Johnson TN, Xu H, et al. Predictive performance of physiologically based pharmacokinetic and population pharmacokinetic modeling of Renally cleared drugs in children. CPT Pharmacometrics Syst Pharmacol. 2016;5:475-483. doi:10.1002/psp4.12101
11. Pemazyre (pemigatinib) [assessment report]. Incyte Biosciences Distribution B.V.; 2021.
12. Penzak SR, Shen JM, Alfaro RM, Remaley AT, Natarajan V, Falloon J. Ritonavir decreases the nonrenal clearance of digoxin in healthy volunteers with known MDRI genotypes. Ther Drug Monit. 2004;26:322-330. doi:10.1097/00007691-200406000-00018
13. Somogyi A, Stockley C, Keal J, Rolan P, Bochner F. Reduction of metformin renal tubular secretion by cimetidine in man. Br J Clin Pharmacol. 1987;23:545-551. doi:10.1111/j.1365-2125.1987.tb03090.x
14. Ji T, Chen X, Liu X, Yeleswaram S. Population pharmacokinetics analysis of pemigatinib in patients with advanced malignancies. Clin Pharmacol Drug Dev. 2022;11:454-466. doi:10.1002/cpdd.1038
15. Greiner B, Eichelbaum M, Fritz P, et al. The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. J Clin Invest. 1999;104:147-153. doi:10.1172/JCI6663
16. Budha NR, Ji T, Musib L, et al. Evaluation of cytochrome P450 3A4-mediated drug–drug interaction potential for cobimetinib using physiologically based pharmacokinetic modeling and simulation. Clin Pharmacokinet. 2016;55:1435-1445. doi:10.1007/s40262-016-0412-5
17. Templeton I, Ravenstijn P, Sensenhauser C, Snoeys J. A physiologically based pharmacokinetic modeling approach to predict drug–drug interactions between domperidone and inhibitors of CYP3A4. Biopharm Drug Dispos. 2016;37:15-27. doi:10.1002/bdd.1992
18. Yoshida K, Budha N, Jin JY. Impact of physiologically based pharmacokinetic models on regulatory reviews and product labels: frequent utilization in the field of oncology. Clin Pharmacol Ther. 2017;101:597-602. doi:10.1002/cpt.622
19. Almond LM, Mukadam S, Gardner I, et al. Prediction of drug–drug interactions arising from CYP3A induction using a physiologically based dynamic model. Drug Metab Dispos. 2016;44:821-832. doi:10.1124/dmd.115.066845
20. Srinivas NR. Pharmacokinetic interaction of rifampicin with oral versus intravenous anticancer drugs: challenges, dilemmas and paradoxical effects due to multiple mechanisms. Drugs R D. 2016;16:141-148. doi:10.1007/s40268-016-0133-0

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