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ARTICLE

Population pharmacokinetics for oral paclitaxel in patients with advanced/metastatic solid tumors

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Abstract

Oraxol consists of an oral dosage form of the chemotherapeutic agent paclitaxel administered with a novel P-glycoprotein inhibitor encequidar methanesulfonate monohydrate (formerly named HM30181A), which allows oral treatment of cancers that would otherwise be treated with intravenous paclitaxel. Here we describe the population pharmacokinetics (popPK) analyses for oral paclitaxel in patients with advanced/metastatic solid tumors to characterize pharmacokinetic (PK) profiles and quantify sources of PK variability. The best fit popPK model for oral paclitaxel, based on data from seven clinical studies (197 patients with advanced/metastatic solid tumors), involves a linear two-compartment structural model containing first-order absorption with a short lag time and first-order elimination as well as a log additive error. In this popPK model, lower population estimates of central volume for Asian patients versus Caucasian patients did not translate into clinical meaningful differences in oral paclitaxel exposure. Age, sex, body weight or surface area, mild hepatic impairment, and mild to moderate renal impairment had no clinically meaningful effects on the systemic exposure of oral paclitaxel. Simulations were performed on clinical therapeutic dose (oral paclitaxel 205 mg/m^2 once daily ×3 days per week) to predict exposure of oral paclitaxel and to support treatment benefits observed in a pivotal phase III trial.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

With intravenous (i.v.) paclitaxel administration, the pharmacokinetics (PK) of paclitaxel were two or three (nab-paclitaxel) compartments with nonlinear clearance structure and body size as the clinical meaningful covariate. No population PK models were reported for the novel formulation of oral paclitaxel.

WHAT QUESTION DID THIS STUDY ADDRESS?

Can the therapeutic dose of oral paclitaxel achieve area under the concentration–time curve comparable to i.v. paclitaxel and support the efficacy of oral paclitaxel observed in clinical trials?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Population models describe PK and characterize between-subject variability (BSV) on PK parameters as well as identify significant covariates that contribute to BSV for oral paclitaxel. Simulations on clinical dose (oral paclitaxel 205 mg/m^2 once daily ×3 days per week) predicted paclitaxel exposure comparable with that of i.v. paclitaxel 175 mg/m^2 q3w and supported treatment benefits observed in pivotal phase III trial.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Oral paclitaxel can be successfully administered with a P-glycoprotein inhibitor, opening new therapeutic options as well as oral formulations of other chemo-agents.

INTRODUCTION

Paclitaxel is a chemotherapeutic agent that is indicated for the treatment of a number of types of cancer, including ovarian cancer, breast cancer, lung cancer, Kaposi sarcoma, cervical cancer, and pancreatic cancer, via a mechanism of stabilizing microtubules and arresting cancer cell division.[1] Paclitaxel is a P-glycoprotein (P-gp) substrate that leads to an efflux of paclitaxel back into the intestinal lumen, thereby making the drug practically nonbioavailable when taken orally. Its poor absorption through the intestinal epithelium has necessitated intravenous (i.v.) administration of paclitaxel. Current commercial i.v. paclitaxel formulations include Taxol (Bristol-Myers Squibb) (caster-oil based), Abraxane (Celgene) (albumin nanoparticles), Lipusu (Luye Pharma) (liposome-based form approved in China), and Genexol-PM (Samyang Pharmaceuticals) (polymer micelle form approved in the Republic of Korea).[2] Furthermore, poor solubility of paclitaxel has necessitated the use of specialized techniques to formulate an i.v. solution; however, the use of excipients such as Cremophor® in the i.v. formulation may cause tolerability problems and increase the incidence of serious adverse events.[3]

A promising new formulation of paclitaxel is an oral dosage form of paclitaxel administered with a highly selective and gastrointestinal (GI) locally active novel P-gp inhibitor, encequidar (in a salt form of encequidar methanesulfonate monohydrate 15-mg tablet, formerly called HM30181A), allowing intestinal absorption and systemic exposure of paclitaxel at therapeutic levels after oral administration and providing a more convenient and safe method of administration. Encequidar, as a locally active agent for GI P-gp inhibition, exhibited minimum systemic exposure (at a nanomolar level) in clinical studies, thus pose a low safety risk.[4]

Patients with advanced/metastatic solid tumors, including advanced/metastatic or recurrent gastric cancer, metastatic breast cancer (MBC), lung cancer, and others, were treated with oral paclitaxel and encequidar (oPac+E). A clinical pharmacokinetics (PK) bioavailability study showed that encequidar 15-mg tablet plus oral paclitaxel 205 mg/m^2 administered for 3 consecutive days can produce a systemic paclitaxel area under the concentration–time curve (AUC) similar to that of 80 mg/m^2 i.v. paclitaxel as a 1 h infusion while the maximum plasma concentration (C_{max}) for oral paclitaxel was approximately one-seventh of i.v. paclitaxel. This may provide advantageous PK profiles to achieve sufficient AUC exposure while mitigating C_{max}-driven toxicities.[5] In the pivotal randomized phase III trial (KX-ORAX-001) of a total of 402 patients with MBC, patients randomly assigned to the oral paclitaxel oPac+E arm had a lower incidence and severity of neuropathy compared with the reference regimen of i.v. paclitaxel, 175 mg/m^2 in 3-h infusions every 3 weeks: 16% of i.v. paclitaxel patients experienced neuropathy (all grades) versus 2% of oral paclitaxel oPac+E patients, with Grade 3 neuropathy observed in 8% of i.v. paclitaxel patients versus 1% of oral paclitaxel oPac+E patients. In addition, the oral paclitaxel oPac+E arm showed a statistically significant higher confirmed tumor overall response rate (the primary efficacy end point) of 36% compared with 24% for i.v. paclitaxel patients ($p = 0.01$).[6]

In two early clinical studies, 68 patients were treated with oral administrations of paclitaxel i.v. solution or liquid-filled capsules with doses ranging from 60 to 420 mg/m^2. Further two dose-finding and two bioavailability studies evaluated the PK, efficacy, and safety profiles of oral paclitaxel in 98 adult patients with cancer ranging from a 270-mg flat dose (approximately 150 mg/m^2 assuming a body surface area [BSA] of 1.8 m^2) to 313 mg/m^2 once daily

(q.d.) ×2 up to ×5 (dose finding), or 205 mg/m^2 from day 1 to day 3 on week 1, and over at least 4 weeks of treatments (bioavailability studies).

Population PK (popPK) modeling is a crucial tool in drug development to quantify drug exposure that could also potentially be used in exposure–response analyses and to identify significant influencing covariates as well as to optimize posology. The popPK of i.v. paclitaxel formulations have been previously reported, but not for our novel oral paclitaxel drug product. Here, we (1) describe the popPK analyses of oral paclitaxel across multiple cancer types in seven clinical trials, (2) assess the impact of intrinsic and extrinsic factors that affect the PK of oral paclitaxel, and (3) simulate exposures in patients with MBC treated with oral paclitaxel. These quantitative analyses supported the recommended posology for oral paclitaxel, including a dose-reduction strategy for treatment-related toxicities.

MATERIALS AND METHODS

Study population

Pooled data of seven clinical studies of oral pacltiaxel were used for the current analysis. The included studies provided sufficient data to support the development of the PK model and also ensured that the findings of the analyses would be relevant to the population of interest, that is, patients with solid malignancies. All studies were approved by the institutional review boards in the Republic of Korea or United States or the Health and Disability Ethics Committee in New Zealand and were performed in compliance with the Declaration of Helsinki.

Bioanalytical methods

Plasma samples for determination of paclitaxel concentrations were analyzed by a validated liquid chromatography with tandem mass spectrometry assay. The lower limit of quantitation (LLOQ) for paclitaxel was 0.25 ng/ml for early studies conducted in Korea (assay developed by Hanmi Pharmaceutical), 1 ng/ml for studies conducted in the United States (assay developed by Wuxi Apptec, previously Xenobiotic Laboratories), and 2.5 ng/ml for studies conducted by Zenith Technology (studies KX-ORAX-002, KX-ORAX-003, KX-ORAX-007 conducted in New Zealand, Australia, and Taiwan). Although the three different bioanalytical methods with varying LLOQ might impact residual error models, the most rich and critical PK data to describe absolute bioavailability, comparability with i.v. paclitaxel, and sustainability of long-term treatment used the Zenith method and hence the impact is trivial.

Data set assembly

A PK analysis data set was prepared based on the individual study plasma paclitaxel data using SAS® (SAS Institute). The data set includes dosing records and paclitaxel concentration records from the completed HM-OXL-101, HM-OXL-201, ORAX-01-13-US, ORAX-01-14-NZ, KX-ORAX-002, and KX-ORAX-007 studies as well as the ongoing KX-ORAX-003 study. A complete list of the variables included in the NONMEM® input data set used to estimate the PK parameters and evaluate the effect of potential covariates on these parameters is provided in Table S2. Given the small number of postdose observation samples below the lower limit of quantitation (BLQ; <1%), the BLQ values following a measurable concentration were set to missing[7] and excluded from the analysis. For covariates with a missing baseline value, the screening value was used. Otherwise, if a screening value was also not available, the covariates were set as missing values. If the proportion of missing covariate values was large (>10%), the analysis of the influence of the covariate was evaluated only as an exploratory analysis.

Software and hardware

Nonlinear mixed-effect modeling was performed using NONMEM® (ICON) 7.3 in the KIWI environment (KIWI 3.0; Cognigen) on a grid of Intel Xeon servers running the CentOS 7 Linux with Open Grid Scheduler, GNU Fortran Compiler (Version 4.8.5), and Perl-speaks-NONMEM (PsN,[8] Version 4.8.1). Descriptive and inferential statistics other than nonlinear mixed-effect modeling were calculated using R 3.6.0 (R Foundation for Statistical Computing). Noncompartmental analyses (NCAs) were performed using WinNonLin 8.0 (Phoenix WinNonLin, Certara). The R package mrgsolve was used to perform PK simulations. The R package ggplot2, WinNonLin 8.0, and/or Microsoft® Office Excel and Powerpoint 2010 were used for producing plots and figures and managing tabular data. The algorithm referred to as first-order conditional estimation without or with interaction was used for parameter estimation.

Structural and statistical model

PK model

Models with one, two, or three compartments were evaluated to describe the PK profiles of paclitaxel. For the absorption phase, a first-order absorption rate with or without a lag time was tested. The compartmental

models were parameterized using apparent clearance(s) and volume(s) of distribution as well as other appropriate parameters (e.g., F1 for the bioavailability fraction).

Between-subject variability model

The variability between individuals in each parameter of the model (e.g., apparent clearance CL/F) was regarded as a random quantity and was modeled in terms of ETA (η) variables. Each η variable was assumed to have a mean of zero and an estimated variance ω^2 describing the BSV of the PK parameter. The inclusion of BSV (reported as a percent coefficient of variation) terms was evaluated in all PK parameters using an exponential form to confine the parameters above zero, as follows:

$$\theta_i = TV\_\theta \times \exp\left(\eta_i\right)$$

where θ_i = the value of the parameter θ for the ith patient, referred to as an empirical Bayes estimate (EBE); TV_θ = the typical population value of the parameter θ; η_i = the individual deviance from the typical population value of the parameter θ, distributed as $\eta_i \sim N(0, \omega^2_\theta)$.

Shrinkage in EBEs was calculated for model diagnostic purposes. Diagnostic plots based on EBEs are more reliable when shrinkage is small.[9,10] Shrinkage magnitude in structural parameters (η-shrinkage) was calculated as:

$$\eta_P - \text{shrinkage} = 1 - \left(SD\left(\eta_{P\_i}\right)/\omega_P\right)$$

where η_P-shrinkage is the shrinkage in model parameter P, $SD(\eta_{P\_i})$ is the standard deviation (SD) of the η_i values for parameter P, and ω_P is the model estimate of interindividual variability associated with parameter P.

Residual error model

Different residual error model structures were evaluated (additive, proportional, proportional + additive, and the additive model in logarithmic scale [log additive]). The residual error model providing the best fit to the data was selected.

Covariate analysis

The effects of covariates were evaluated using a stepwise forward selection, full multivariable model evaluation, followed by a backward elimination covariate selection model-building procedure based on the subset of covariates identified during the exploratory graphical analysis as relevant (e.g., ETA vs. covariates), when the ETA-shrinkage value was lower than 30%.[11-14] Linear, exponential, and power models were tested to describe the continuous covariate associations. For instance, forward selection with a linear relation adds one degree of freedom and requires an improvement of objective function value (OFV) >6.64 associated with a p value < 0.01 to be considered for statistical significance. The backward elimination proceeds as the forward selection but in reverse using stricter criteria for model improvement, namely, a loss in OFV of no more than 10.83 ($p < 0.001$) is required to confirm that the covariate is not significant.

Model selection criteria

Models were compared on the basis of OFV. The ability of the population model to describe the data was also assessed by graphical analysis. The following goodness-of-fit (GoF) diagnostic plots (including but not limited to) were evaluated: observations versus population or individual predictions, conditional weighted residuals (CWRES) or individual weighted residuals (IWRES) versus time, and individual plots comparing observed and individual predictions over time.

Relative standard error (RSE) of the parameters were also checked for model selection criteria. In addition, mean and median η values were examined to ensure that they were centered at zero and showed no large deviance from 0 (namely, etabar close to 0).

Final PopPK model

The final model was qualified by meeting the following criteria: (1) minimization and the covariance step obtained successfully in NONMEM® (in the case in which covariance could not be computed, the standard error was to be estimated using a nonparametric bootstrap), (2) at least three significant figures obtained for all θ estimates, (3) the standard error of θ estimates preferably <30% and the standard error of η estimates preferably <50% of the estimate itself, (4) the shrinkage computed for η estimates preferably <30%, and (5) no unacceptable trends in the GoF plots.

Model evaluation predictive performance

Visual predictive check

The predictive performance of the popPK model was evaluated by performing a visual predictive check (VPC)[8,15,16]

to verify the agreement between observed data and values simulated using the popPK model. Model parameters were randomly sampled from their estimated distributions, and plasma concentrations for oral paclitaxel were simulated using the sampled PK parameter values and residual variability. For each individual, the covariate values, dosing information, and sampling times were identical to those contained in the original data set used for model development. The simulation was repeated 1000 times for the entire data set. For each simulation run, the median and the 5th and 95th percentiles were obtained. Then for each of these three statistics, the 90% intervals were extracted from results of the 1000 simulation runs and displayed on the graph as shaded areas. The median and the 5th and 95th percentiles derived from the observed data were then superimposed on the same graph and compared with the 90% prediction intervals. Specifically, the prediction-corrected VPC (pcVPC) was used to evaluate the predictive performance of the model via normalizing the observed and simulated dependent variable based on the typical population prediction for the median independent variable in the bin, thus removing the variability coming from binning across independent variables.

Bootstrap

A nonparametric bootstrap resampling approach was used to qualify the final selected popPK model and confirm the stability and robustness of final population estimates. A total of 1000 replicates of the data set were generated by bootstrap resampling, and the popPK model was fit to each replicate. Based on the parameter estimates obtained from each of the bootstrap model fits, the median and 5th and 95th percentiles (empirically equivalent to a 95% confidence interval [CI]) of each PK parameter and fixed-effect and random-effect parameter were calculated. The parameter estimates from the final popPK model were compared with the bootstrap results (median and 90% CI).

EBE for individual parameters

The EBEs of individual PK parameters were used to predict PK concentrations and exposures, which were further evaluated for clinical exposure comparisons between Asian/non-Asian patients. Plots of predicted concentrations were used to illustrate the presence or absence of a marked difference in exposure levels in Asian versus non-Asian patients. Boxplots illustrating the differences in EBE-based exposure estimates between patient subgroups were also generated for assessing the clinical relevance of covariate effects.

Simulations for the two different dosage forms

Based on the final model, concentrations were simulated for 1000 individuals (500 Asian/500 non-Asian) using the R package mrgsolve, and PK parameters were calculated by NCA methods in Phoenix WinNonLin using simulated concentrations. The figures were generated from the R package ggplot2. Population simulations were performed with the aim of predicting individual plasma concentration–time profiles for paclitaxel: (1) 205 mg/m^2 q.d. ×3/week oral dosing and (2) 175 mg/m^2 q3w i.v. dosing. Oral PK sampling schedules for simulations were (1) predose samples for each dose (0, 24, 48 h), (2) every 1 h for 1–4 h post each dose (1, 2, 3, 4, 25, 26, 27, 28, 49, 50, 51, 52), and (3) every 24 h post third dose up to 168 h (72, 96, 120, 144, 168).

Assumptions

The date, time, actual amount of drug intake, and actual PK sampling times were assumed to be recorded accurately. It was also assumed that there were no significant differences in assay sensitivity and accuracy for plasma PK concentration measurements among the bioanalytical vendor laboratories used in these pooled studies.

RESULTS

PopPK analysis data sets

The characteristics of all studies (HM-OXL-101, HM-OXL-201, ORAX-01-13-US, ORAX-01-14-NZ, KX-ORAX-002, KX-ORAX-003, and KX-ORAX-007) and patient flow such as dosing arms (expected number of patients), regimens, number of patients included in the popPK analysis, PK sampling schedules, and expected number of blood samples are summarized in Table S1. PK data from 197 patients with cancer in these seven studies provided a total of 6429 records, consisting of 2107 dosing records and 4322 paclitaxel plasma concentration records in the popPK analyses data set. No patient was impacted by missing sampling times. A total of 28 postdose records were excluded from the analyses as a result of being BLQ. Mean age was 59.6 years (range, 32–81 years), 47.7% of patients were male, 55.8% were Asian, and 41.1% were Caucasian (Table 1). Mean albumin concentration, creatinine clearance (CRCL; estimated using Cockcroft–Gault formula), and total bilirubin concentration were 39.1 g/L (range, 23–51 g/L), 88 ml/min (range, 33–230 ml/min), and 0.6 mg/dl (range, 0.12–2.0 mg/dl), respectively. Gamma-glutamyltransferase and alkaline phosphatase were more variable with mean

TABLE 1 Demographics and baseline characteristics for patients from seven studies

Total patients in analysis ($N = 197$)	
Sex, *n* (%)	
Male	94 (47.7)
Female	103 (52.3)
Age, years	
Mean (SD)	59.6 (10.7)
Range	32.0–81.0
Age group, *n* (%)	
<65 years	127 (64.5)
≥65 years	70 (35.5)
Race, *n* (%)	
Asian	110 (55.8)
Caucasian	81 (41.1)
African American	4 (2.0)
American Indian	1 (0.5)
Native Hawaiian or Other Pacific	1 (0.5)
Weight, kg	
Mean (SD)	67.2 (15.9)
Range	38.0–139.0
Body surface area, m^2	
Mean (SD)	1.73 (0.23)
Range	1.29–2.46
Albumin, g/L	
Mean (SD)	39.1 (5.3)
Range	23.0–51.0
Creatinine clearance, ml/min[a]	
Mean (SD)	88 (33)
Range	33–230
Total bilirubin, mg/dl	
Mean (SD)	0.6 (0.34)
Range	0.12–2.0
Alkaline phosphatase, U/L	
Mean (SD)	125 (104)
Range	32–873
Alanine aminotransferase, U/L	
Mean (SD)	23.5 (15.5)
Range	3.0–85.0
Aspartate aminotransferase, U/L	
Mean (SD)	66.2 (16.3)
Range	32–222
GGT, U/L[b]	
Mean (SD)	32.0 (23.7)
Range	9.0–203.0
Renal function, *n* (%)	
Normal	79 (40.1)
Mild impaired	85 (43.1)
Moderate impaired	33 (16.8)
Hepatic function, *n* (%)	
Normal	177 (89.8)
Impaired	20 (10.2)
Formulation, *n* (%)	
Oral solution	15 (7.6)
Oral capsule	182 (92.4)

Note: Total patients in analysis = 197. The table provides the patient counts for categorical covariates and the summary statistics for the continuous covariates for all patients in the data set.Abbreviations: GGT, gamma-glutamyltransferase; SD, standard deviation.

[a]Creatinine clearance was calculated using the Cockcroft–Gault equation.

[b]One patient data was missing for GGT. During the pharmacokinetic modeling, the population median values were used for this patient.

concentrations of 32.0 U/L (range, 9.0–203.0 U/L) and 125 U/L (range, 32–873 U/L), respectively. The majority of patients were treated with the capsule formulation of oral paclitaxel (92.4%), 10.2% of patients had mild hepatic impairment (based on National Cancer Institute-Organ Dysfunction Working Group [NCI-ODWG] criteria), and 43.1% and 16.8% of patients had mild or moderate renal impairment, respectively (Table 1).

Oral paclitaxel popPK model

The structural model for oral paclitaxel PK was a linear two-compartment model with first-order absorption with a lag time and first-order elimination as well as a log additive error. One, two, or three compartment models with additive or proportional error structures were initially tested during the development of the base structural PK model; however, those models were inferior in fitting the data compared with the selected structural model.

After the base model was established, the 19 covariates (Table S2) in the popPK data set were explored graphically using ETA (η) versus categorical or continuous covariates plots as well as plots between covariates to identify correlations. Based on this evaluation, a subset of covariates was identified as relevant and having the potential to affect the model: (1) formulation, weight, race, and encequidar dosing time on bioavailability (F1); (2) weight, sex, and race on apparent clearance (CL/F); (3) weight, BSA, albumin, race, and sex on central volume of distribution (V2) (Table S3). Because body weight and BSA were significantly correlated with height ($r > 0.6$), only body weight or BSA was tested for the covariate effects, and incorporated into the model, if appropriate.

As a result in the final model, significant covariates included the effects of race on V2, and effect of formulation

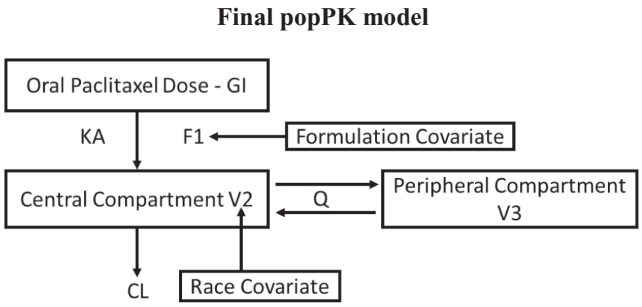


FIGURE 1 Oral paclitaxel final popPK model. CL, central clearance; F1, bioavailability; GI, gastrointestinal; KA, absorption rate constant; popPK, population pharmacokinetic; Q, intercompartmental clearance; V2, central compartment volume of distribution; V3, peripheral compartment volume of distribution

on bioavailability (F1). The final popPK model structure is depicted in Figure 1 and population parameters estimations are presented in Table 2.

The bioavailability (F1) was fixed to 0.119 in the patients treated with the oral paclitaxel capsule formulation. The oral paclitaxel solution (bioavailability estimated to be 0.226) was used only in the very first trial, and current formulations for late-phase trials or commercialization are solid dosage forms (capsule or tablet).

V2 was estimated to be greater for non-Asian (mostly Caucasian) (i.e., $50.7\times(1+0.696) = 86.0$ L) patients in comparison with approximately 50.7 L in Asian patients. Based on the low ETA shrinkage, the lack of misfit in the GoF diagnostic plots, the adequate precision of the parameters, and the satisfactory VPCs, the EBEs of the individual parameters were thus considered suitable for estimating individual concentrations and exposure parameters to evaluate clinical exposure estimates between Asian versus Caucasian patients who received the oral capsule paclitaxel formulation.

Overall, the data suggest comparable exposure by AUC and C_{max} between Asian and Caucasian patients with <20% differences, and central clearance was similar between male and female patients (Figure 2a). Although the race covariate effect incorporated in the final model was considered statistically significant, the aforementioned results illustrate that the covariate effect is not likely to impact the clinical exposure of oral paclitaxel, as the exposure alteration of 20% or less is predicted (given that AUC is a key factor in clinical responses for paclitaxel).

The popPK data set included 94 men (47.7%) and 103 women (52.3%). Sex was not identified as a statistically significant covariate on PK parameters including CL/F and V2; thus, there was no clinically meaningful influence on the distribution or clearance of oral paclitaxel. Age was not identified as a significant covariate influencing

TABLE 2 Oral paclitaxel final PK model parameters

Parameter	Estimate	RSE, %	Shrinkage (%)
Population			
CL (L/h)[a]	33.7	4.2	34.4 (29.8)
V2 (L)	50.7	15.9	176 (13.0)
Q (L/h)	40.6	5.1	48.0 (15.0)
V3 (L)	855	4.9	–
KA (1/h)	0.724	5.2	–
ALAG1 (h)	0.215 (fixed)		–
F1	0.119 (fixed)		–
Covariates			
Race on V2 (proportional)	0.696	36.6	–
Formulation on F1 (proportional)	0.895	28.5	–
Interindividual variability			
ETA CL (CV%)	34.4	25.8	29.8
ETA V2 (CV%)	176	27.0	13.0
ETA Q (CV%)	48.0	19.6	15.0
Residual variability			
Log additive	0.208	6.6	–
OFV		1279.4	
Condition number		34.793	

Abbreviations: ALAG1, absorption lag time; CL, central clearance; CV, coefficient of variation; F1, bioavailability; KA, absorption rate constant; OFV, objective function value; PK, pharmacokinetic; Q, intercompartmental clearance; RSE, relative standard error; V2, central compartment volume of distribution; V3, peripheral compartment volume of distribution.

[a]Apparent clearance = CL/F where F is fixed in the modeling.

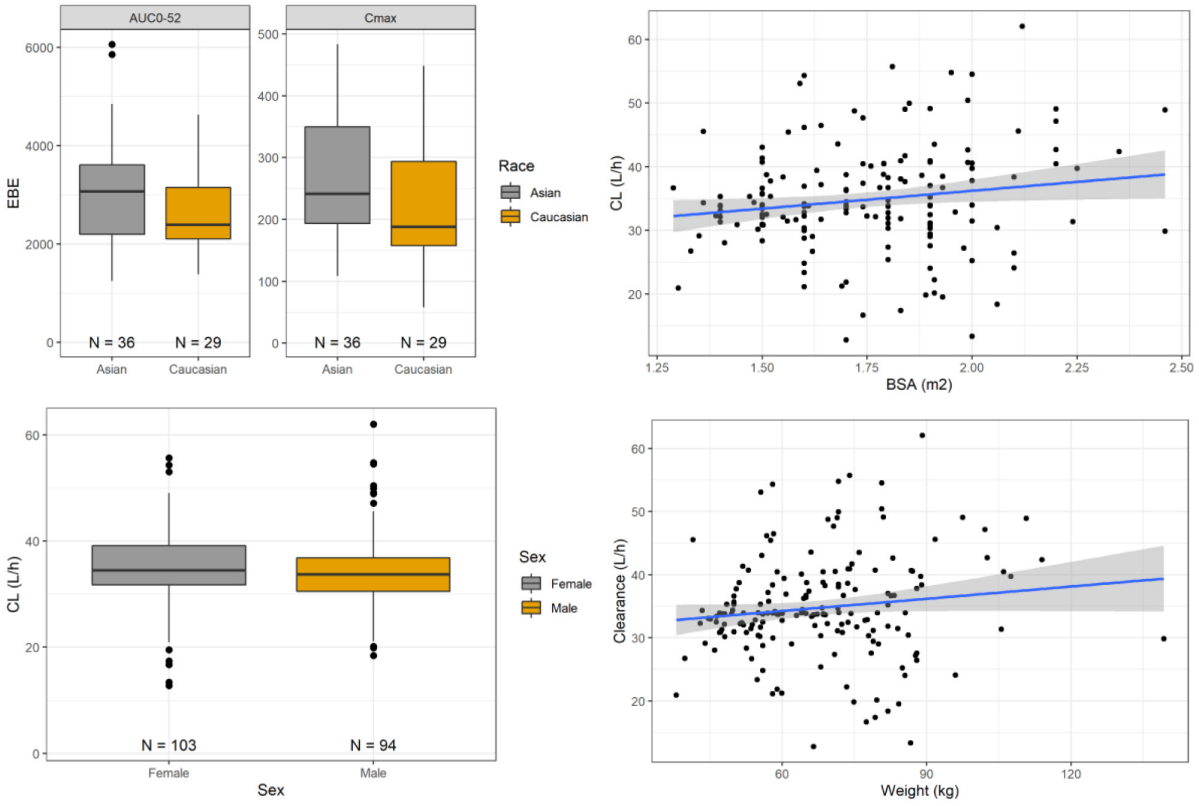
oral paclitaxel PK based on the popPK analysis, which included patients ranging from 32 to 81 years of age ($n = 197$), with a mean and median of 60 years of age. Age group (≥65 years [$n = 70$] or <65 years [$n = 127$]) was also not identified as a significant covariate, indicating no PK differences associated with elderly patients.

Based on this popPK analysis that included patients treated with oral paclitaxel under a fasted condition ($n = 191$, 97%) and uncontrolled prandial state ($n = 6$, 3%), data are not sufficient for drawing a conclusion regarding the effect of food. The effects of food on the PK of oral paclitaxel are still under investigation by a dedicated food-effect clinical study (i.e., KX-ORAX-012).

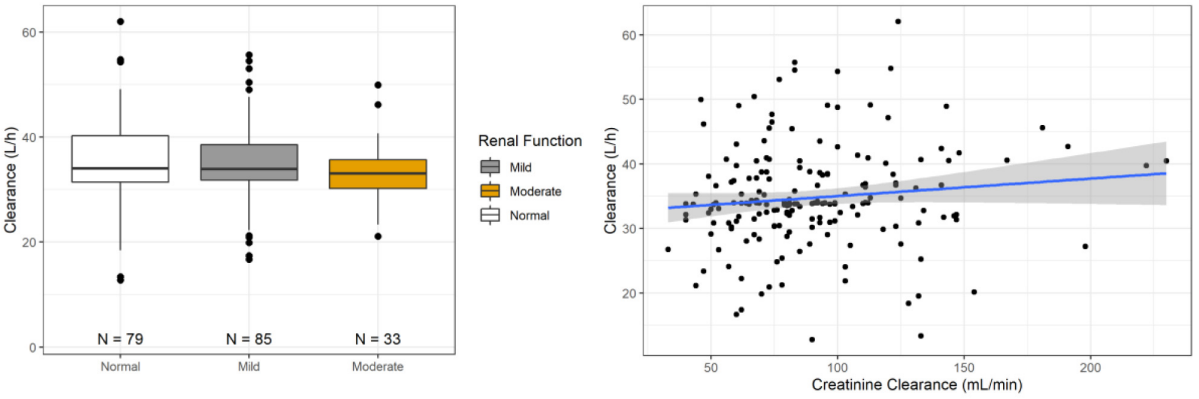
Other covariates, including body weight and BSA (Figure 2a), liver enzymes (other than aspartate aminotransferase [AST]), and albumin levels, did not reach statistical significance on the PK parameters, including the distribution or apparent clearance of oral paclitaxel.

Paclitaxel is primarily metabolized and subsequently cleared by the liver with very little renal clearance. In agreement with this, based on this popPK analysis that

(a) PK Parameters



(b) renal impairment



(c) hepatic impairment

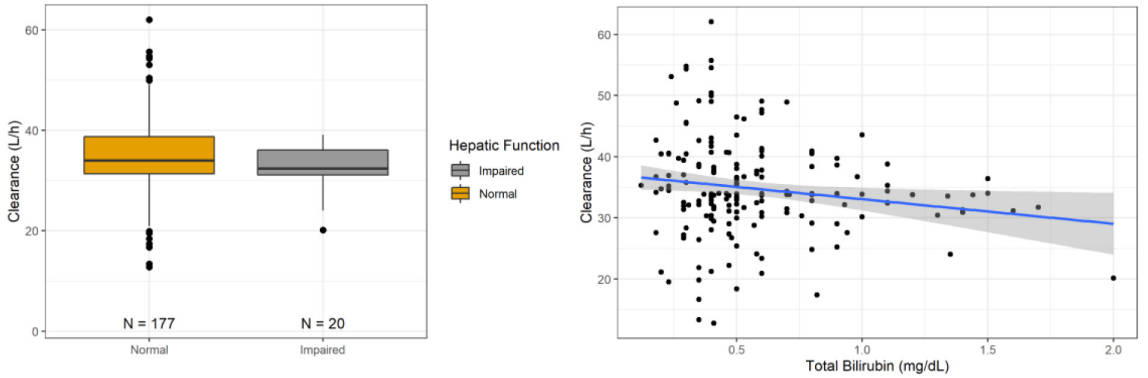


FIGURE 2 Covariate effects on pharmacokinetic parameters. (a) Pharmacokinetic clearance versus demographics or exposure parameters (maximum plasma concentrations/area under the concentration-time curve) comparisons for Asian versus Caucasian patients from EBE estimation. All data were for oral capsule paclitaxel formulation only. Data on clinical dose 205 mg/m^2 with once daily ×3 regimen were used to compare maximum plasma concentrations and area under the concentration–time curve between Asian versus Caucasian patients. (b) Boxplots of renal impairment on clearance and scatterplots of clearance versus creatinine clearance. (c) Boxplots of hepatic impairment on clearance and scatterplots of clearance versus total bilirubin. CL, clearance; EBE, empirical Bayes estimate

included patients with normal renal function (n = 79; CRCL, ≥90 ml/min) and mild (n = 85; CRCL, 60–89 ml/min) and moderate (n = 33; CRCL, 30–59 ml/min) impairment, the effect of CRCL on oral paclitaxel was minor and not expected to be clinically meaningful (Figure 2b). Data are unavailable to make any inferences on patients with severe renal insufficiency.[17]

Based on this popPK analysis including patients with normal (n = 177) and mildly impaired hepatic function, the effect of hepatic function (including AST and total bilirubin) on oral paclitaxel was also minor and not expected to be clinically meaningful (Figure 2c). Of the 20 patients with hepatic impairment, there were 19 patients with mild (nine mild Group B1 and 10 mild Group B2 categories) and one with moderate impairment based on the subcategories of NCI-ODWG criteria on hepatic dysfunction[18]; therefore, data are not sufficient for drawing a conclusion regarding patients with moderate or severe hepatic insufficiency.

PopPK model evaluation

A subset of the diagnostic plots is presented in Figure 3a. Overall, diagnostic plots showed tight normal scatter around the line of identity and indicated that the final PK model fit the data well with the absence of significant bias. The plots of CWRES versus time and IWRES versus model predictions showed a random distribution of data points around the zero line, confirming that the model developed is sufficient to characterize the time course of oral paclitaxel concentrations. Representative observed, individual prediction, and population prediction plots are shown in Figure 3b, indicating a good population or individual predictions over observed data. The plot of the correlation between the random effects is presented in Figure S1. The correlations are low ($|r| < 0.1$ for ETA1 vs. ETA2 or ETA6; $r = -0.38$ for ETA2 vs. ETA6), indicating that these parameters are sufficiently independent.

Results of the pcVPC for oral paclitaxel (time, 0–168 h) are depicted in Figure 3b (y-axis in log scale; stratified by formulation). Based on the pcVPC plots, the predictive performance of the final PK model for oral paclitaxel was considered to be satisfactory. The central tendency was generally well predicted by the model as the median of the data was within the CI of the simulated data for most time bins. A slight tendency to underpredict the peak of the concentration–time profile (0.5–2 h postdose) was noted. Furthermore, the overall variability was well predicted based on the general agreement between the 5th and 95th percentiles of the data and the corresponding percentiles from the simulation. Therefore, the model was considered as fit for simulation.

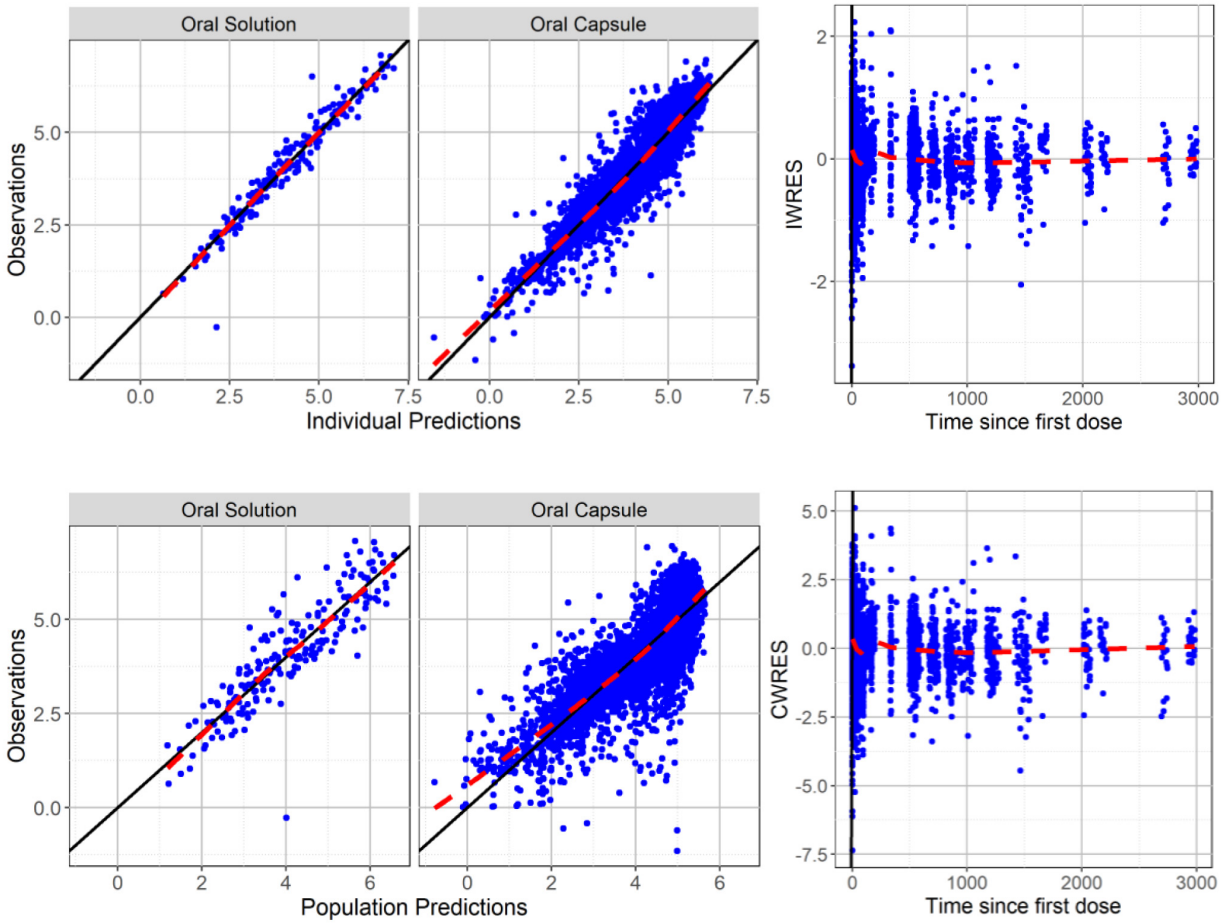
A bootstrap analysis was performed using a total of 1000 replicates of the data set generated by bootstrap resampling, and the popPK model was fit to each replicate. The parameter estimates (RSE percentage) obtained for the final model together with the estimates obtained from bootstrap analysis and the 90% CI are presented in Table S4. The population parameter estimates obtained from the final model and mean of the bootstrap replicates are very similar, and both are contained within the 90% CI of the bootstrap analysis. Thus, the results of the bootstrap analysis confirmed the robustness of the final parameter estimates and the standard errors from the covariance step.

DISCUSSION

This popPK data analysis was conducted and reported in accordance with the current US Food and Drug Administration and European Medicines Agency guidance for industry on popPK analyses and reporting.[19,20] The first objective of the analysis was to describe the PK of oral paclitaxel in patients with advanced/metastatic solid tumors using data from studies conducted in patients with cancer. The data suggested that oral paclitaxel PK was best characterized by a two-compartment model with first-order absorption and elimination as well as a short absorption lag time (0.215 h) and a log additive error structure. All absorption- and disposition-related parameters were well estimated with RSE < 20% (mostly <10%). This two-compartment structure was also consistent with the literature on i.v. paclitaxel PK.[21,22] In addition, nonlinear PK of i.v. pacliataxel was reported.[23] In the Chen et al.[24] article on nab-paclitaxel (Abraxane) PK; however, a three-compartment structure was proposed because of the significant albumin effects on elimination.

The covariates of age (32–81 years), body weight (38–139 kg), surface area (1.29–2.46 m^2), mild hepatic

(a) Diagnostic Plots



(b) pcVPC

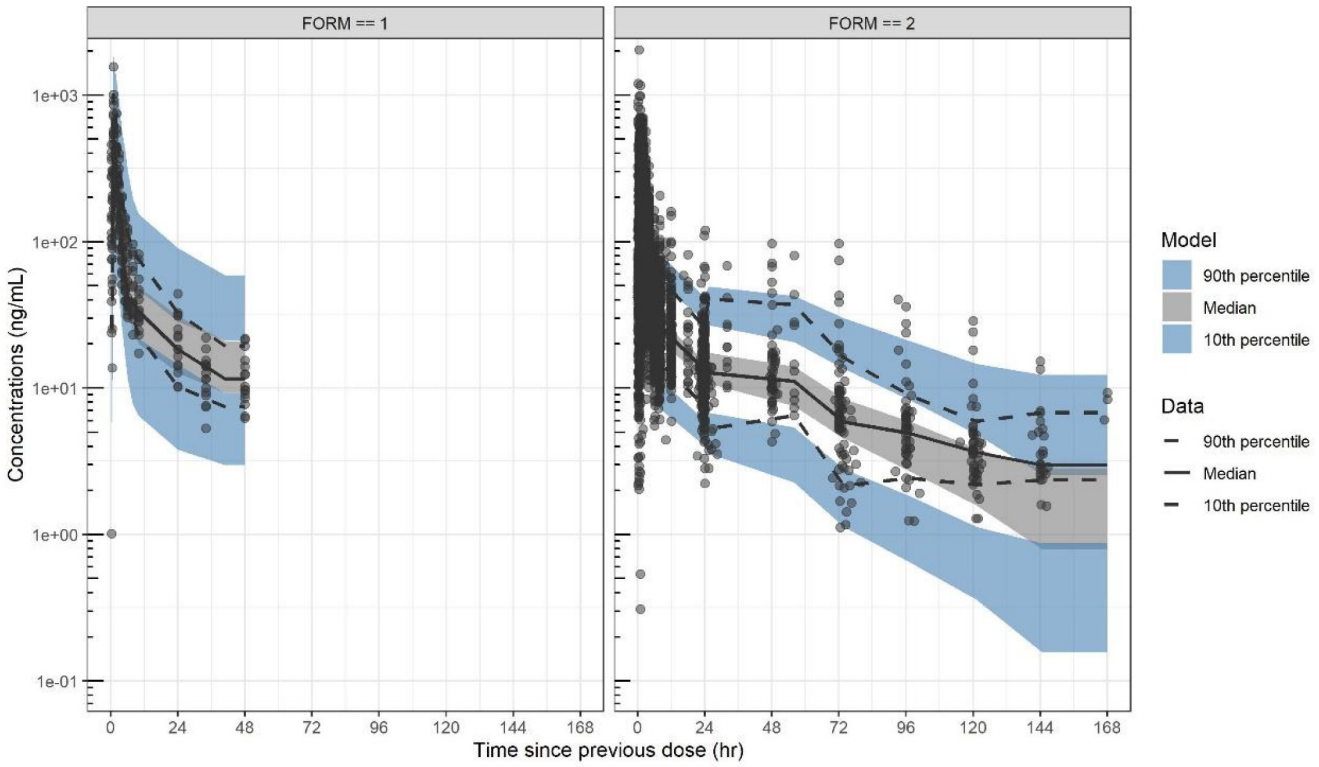
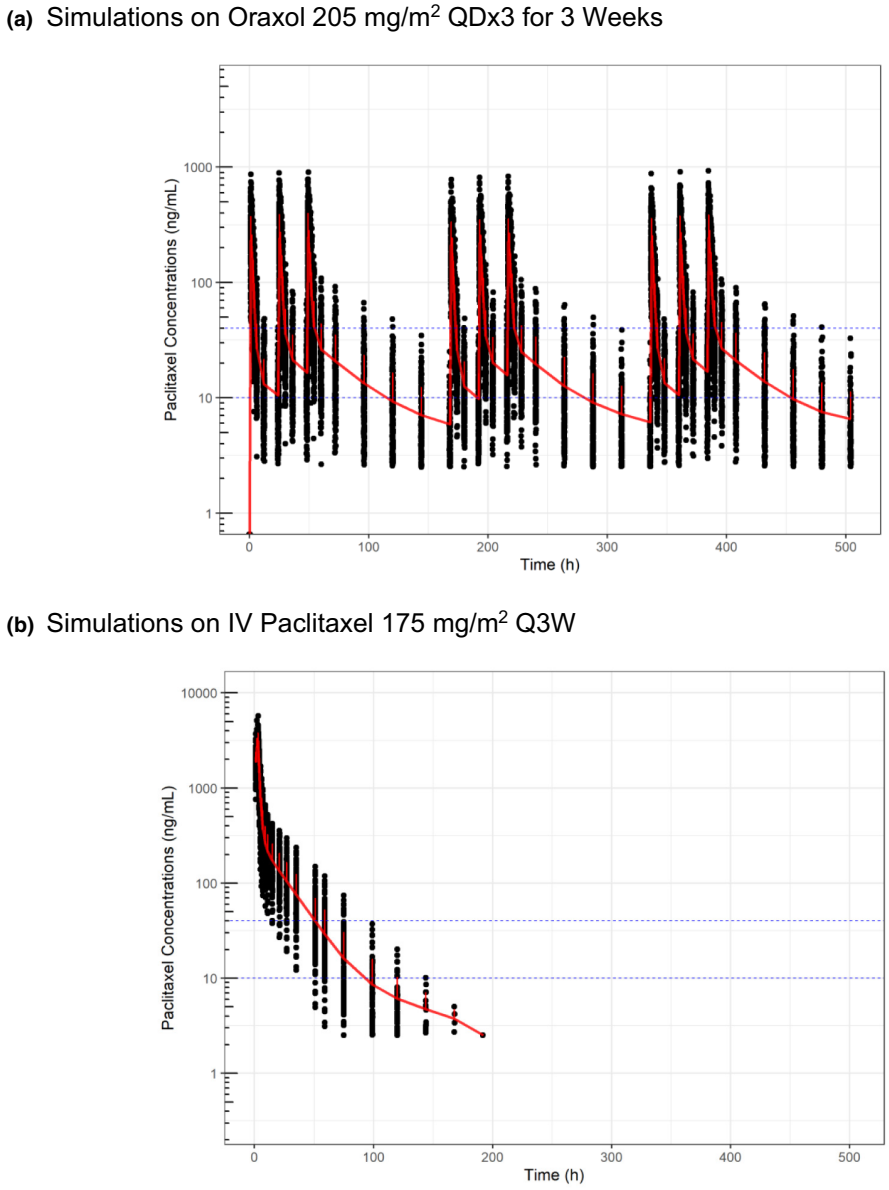


FIGURE 3 Diagnostic plots of the final population pharmacokinetic model. (a) The observations versus individual or population predictions stratified by formulation; the individual weighted residuals (IWRES) or conditional weighted residuals (CWRES) versus time. (b) Prediction corrected visual predictive check (pcVPC) for oral paclitaxel (time after dose). Red lines connect the median and 5th and 95th percentiles per bin of time after dose. Shaded area connects the 95% confidence intervals of the simulated medians and 5th and 95th percentiles. Open circles are prediction-corrected observed concentration data. FORM=formulation (1=solution and 2=capsule)

FIGURE 4 Individual and mean (+ standard deviation [SD]) plots on simulations for oraxol (a) or intravenous (b) treatments in KX-ORAX-001 Study (*y*-axis in log scale). Black dots represent simulated concentrations; red line represents mean concentration-time curve with error bar for +SD. Lower limit of quantitation = 2.5 ng/ml and postdose below the lower limit of quantitation values were set as missing. Two horizontal blue dash lines represent arbitrary thresholds of 40 and 10 ng/ml, respectively



impairment (total bilirubin ≤ upper limit of normal [ULN] and AST > ULN or total bilirubin 1–≤1.5 × ULN and AST any value), mild to moderate renal impairment (CRCL, 30–89 ml/min), race (White and Asian), and sex had no clinically meaningful effect on the systemic exposure of paclitaxel.

The final popPK model was determined to be sufficient to properly describe the PK profiles of oral paclitaxel in adult patients with cancer according to the following characteristics: (1) the lack of bias or misfit evident in the diagnostic plots, (2) the precision of the parameter estimates, and (3) the satisfactory results of the pcVPCs. Furthermore, the model was considered suitable to support the dose justification for comparing different subpopulations and for estimating exposure parameters for future exposure–safety exploratory analyses.

Based on the final model, body size is not a covariate, which could potentially support a fixed-dosing strategy for oral paclitaxel. However, paclitaxel (i.v. formulation) is a

narrow therapeutic-index cytotoxic agent that has been used with a BSA-based dosing regimen for more than 25 years. Hence, the fixed-dosing regimen has to be tested from the early phase, and we have initiated phase I and Ib studies in both mono- and combination-therapy trials.[25,26] These studies should provide further PK, safety, and efficacy data that confirm whether a fixed-dosing strategy would be advantageous and help design late-phase trials.

Before this flat dosing strategy can be implemented, oral paclitaxel phase III study continued the BSA-based dosing strategy. The figures of simulated concentration–time profiles were generated from the R package ggplot2 for following dosage forms: (1) 205 mg/m^2 q.d. ×3/week dosing and (2) 175 mg/m^2 q3w i.v. dosing. The results of simulations are presented graphically in Figure 4 and summarized in Table S5. In the results of the simulations, mean $AUC_{0-504\,h}$ was similar between the oral and i.v. paclitaxel dosing regimens, whereas the time of exposure >0.05 μmoL/L ($T > 0.05$ μM [or 40 ng/ml]) was twice as long with oral than i.v. paclitaxel (Figure 4). It has been reported[22,27] that the response to paclitaxel is related to T > 40 ng/ml.

Oral paclitaxel was consistently and reproducibly absorbed over weeks, and no obvious accumulation was observed from days 1 to 3 or from weeks 1 to 4 as shown in the plots (Figure S2). From the simulated results, the current therapeutic dose of 205 mg/m^2 q.d. ×3/week seems to be reasonable.

In conclusion, a popPK model of oral paclitaxel has been successfully developed and evaluated. This model adequately describes the oral paclitaxel PK in patients with cancer.

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CONFLICT OF INTEREST

J.H., D.K., W-K.C, R.K., D.C., and J.Z. are employees and shareholders of Athenex Inc. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.H., C.G.C.A.J., S.D., T.H., K.C., E.S., T.-Y.C., M.-S.D., H.-T.Y., W.W.M., D.K., W.-K.C., R.K., D.C., and J.Z. wrote the manuscript. D.K., W.-K.C., R.K., and D.C. designed the research. C.G.C.A.J., S.D., K.C., E.S., T.-Y.C., M.-S.D., H.-T.Y., and W.W.M. performed the research. J.H., D.C., and J.Z. analyzed data. T.H. contributed new reagents/analytical tools.

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SUPPORTING INFORMATION

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