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Population Pharmacokinetic Analysis of Pexidartinib in Healthy Subjects and Patients With Tenosynovial Giant Cell Tumor or Other Solid Tumors

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Abstract

Pexidartinib is a kinase inhibitor that induces tumor response and improvements in symptoms and functional outcomes in adult patients with symptomatic tenosynovial giant cell tumor (TGCT). A population pharmacokinetic (PK) model for pexidartinib and its metabolite, ZAAD, was developed, and effects of demographic and clinical factors on the PK of pexidartinib and ZAAD were estimated. The analysis included pooled data from 7 studies in healthy volunteers (N = 159) and 2 studies in patients with TGCT or other solid tumors (N = 216). A structural 2-compartment model with sequential zero- and first-order absorption and lag time, and linear elimination from the central compartment adequately described pexidartinib and ZAAD PKs. Clearance of pexidartinib was estimated at 5.83 L/h in a typical patient with reference covariates (male, non-Asian, weight = 80 kg, creatinine clearance ≥90 mL/min, aspartate aminotransferase ≤80 U/L, and total bilirubin ≤20.5 μmol/L). In the covariate analysis, Asians and healthy subjects had modestly lower pexidartinib exposure (21% decrease each) in terms of steady-state area under the curve values from 0 to 24 hours ($AUC_{0\text{-}24,ss}$). Effects of body weight, sex, and hepatic function parameters on pexidartinib $AUC_{0\text{-}24,ss}$ were generally <20%. Patients with TGCT with mild renal impairment were predicted to have approximately 23% higher $AUC_{0\text{-}24,ss}$ than those with normal renal function. The effects of covariates on ZAAD exposure were similar to those on pexidartinib. These results indicate small and generally clinically nonmeaningful effects of patient demographic and clinical characteristics on pexidartinib and ZAAD PK profiles.

Keywords

pexidartinib, PK, pharmacokinetics, population pharmacokinetics, TGCT, ZAAD

Pexidartinib is a novel oral small-molecule inhibitor that selectively targets colony-stimulating factor 1 receptor, KIT proto-oncogene receptor tyrosine kinase, and FMS-like tyrosine kinase 3, harboring an internal tandem duplication mutation.[1] Pexidartinib is approved in the United States at a dosage of 400 mg twice daily for the treatment of adult patients with severe symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.[2] Due to risk of hepatotoxicity, pexidartinib is available only through the Risk Evaluation and Mitigation Strategies program in the United States.[2]

The pharmacokinetics (PK) of pexidartinib have been evaluated in studies in healthy subjects and patients with TGCT or other solid tumors at doses ranging from 200 mg to 2400 mg.[3] Maximum plasma concentrations (C_{max}) were achieved approximately 2.5 hours after the dose, and pexidartinib exposure, as measured by C_{max} and area under the plasma concentration–time curve (AUC) from time 0 to infinity, increased in a dose proportional manner over this dose range.[3] Administration with a high-fat meal delays the time to C_{max} by 2.5 hours (ie, to 5 hours) and increases pexidartinib C_{max} and AUC from time 0 to infinity by 100%.[3]

The primary metabolic pathway of pexidartinib is oxidation via cytochrome P450 3A4, and glucuronidation via uridine 5′-diphosphoglucuronyltransferase 1A4.[2] ZAAD-1006 (ZAAD) is the primary *N*-glucuronide metabolite of pexidartinib

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Table 1. Summary of Studies Included in Population PK Analysis

Study	Study Design	Subjects	No. of Measurable PK Samples	Description	Pexidartinib Dose Regimen
U114	Phase 1, OL, R, CO	30 healthy subjects	1728	PK study	400-mg single dose
U116	Phase 1, OL, R, CO	36 healthy subjects	1824	PK study	600-mg single dose
U117	Phase 1, OL, R, CO	18 healthy subjects	1119	PK study	200-, 400-, and 600-mg single dose
U118	Phase 1, OL, SS	16 healthy subjects	334	Drug interaction study	600-mg single dose
U119	Phase 1, OL, SS	16 healthy subjects	333	Drug interaction study	600-mg single dose
U120	Phase 1 OL, CO	16 healthy subjects	323	Drug interaction study	600-mg single dose
U121	Phase 1, SB, PC	27 healthy subjects	589	Dose-ranging PK study	1200-, 1800-, and 2400-mg single dose
PLX108-01	Phase 1, OL	132 patients with advanced solid tumors	1726	Dose-escalation PK and PD study	200 mg once daily, escalating to 600 mg twice daily
PLX108-10 (ENLIVEN)	Phase 3, DB, R, PC	84 patients with TGCT	454	Safety/efficacy study	Part 1: 1000 mg/day (400 mg am/600 mg pm) Part 2: 800 mg/day (400 mg twice daily)

CO, crossover; DB, double blind; OL, open label; PC, placebo controlled; PD, pharmacodynamic; PK, pharmacokinetic; R, randomized; SB, single blind; SS, single sequence; TGCT, tenosynovial giant cell tumor.

that is minimally pharmacologically active and has approximately 10% higher systemic exposure than pexidartinib after a single dose to healthy subjects. Excretion of pexidartinib is primarily via the feces as unchanged drug,[2] and pexidartinib exposure is affected by coadministration with a cytochrome P450 3A4 inducer or inhibitor or a uridine 5′-diphosphoglucuronyltransferase 1A4 inhibitor.[2]

The ENLIVEN study (Phase 3 Study of Pexidartinib for Pigmened Villonodular Synovitis [PVNS] or Giant Cell Tumor of the Tendon Sheath [GCT-TS]) was the first randomized, placebo-controlled phase 3 study in patients with histologically confirmed, advanced, symptomatic TGCT. Treatment with pexidartinib for 24 weeks (1000 mg/day for 2 weeks; 800 mg/day for 22 weeks) resulted in compelling tumor responses compared with placebo via response evaluation criteria in solid tumors (39% vs 0%) and tumor volume score (56% vs 0%). In addition, pexidartinib treatment led to improvements from baseline in patient symptoms and functional outcomes such as range of motion and worst stiffness.[4]

The ENLIVEN study included a diverse patient population (age, race, weight, comorbidities), and pexidartinib was administered as prolonged therapy. Thus, it is important to understand the population PK characteristics of pexidartinib, including the intersubject variability and factors that influence PK parameters. The objectives of this analysis were to develop a population PK model for pexidartinib and its metabolite ZAAD in healthy subjects and patients with TGCT and to estimate effects of potential covariates, such as demographic and clinical factors, on the PK of pexidartinib and ZAAD.

Materials and Methods

Data Sources and Study Populations

Pooled data from 9 clinical studies were used for the population PK analysis of pexidartinib (Table 1). These included 7 phase 1 studies in healthy subjects (N = 159), 1 phase 1 study in patients with TGCT or other solid tumors (PLX108-01, N = 132), and 1 phase 3 study (ENLIVEN, PLX108-10) in patients with TGCT (N = 84). The population PK data set for the metabolite ZAAD included 5 phase 1 studies (N = 93) and the ENLIVEN trial (N = 84). There were no ZAAD PK data available in studies U114, U116, or PLX108-01. In all studies, pexidartinib was administered in the fasting state.

Two forms of pexidartinib drug product were used in the clinical studies. Phase 1 formulation was used in the initial stage of the clinical development program. Later, phase 3 formulation was introduced as the "to-be marketed" drug product, and it was used in all other clinical studies involving healthy volunteers and patients. Specifically, studies U114 and PLX108-01 used the phase 1 formulation, whereas all other studies used the phase 3 formulation.

In the phase 1 studies in which single doses of 200 mg to 2400 mg were administered, serial PK samples were collected before dosing and up to 144 or 192 hours after dosing. In study PLX108-01, PK samples were collected before dosing on days 2, 8, and 16 of cycle 1 and at 5 to 6 time points (0.5 to 8 hours after dosing) on days 1 and 15 of cycle 1. In the ENLIVEN trial, PK samples were collected before dosing on days 1 and 15 and 0.5, 1, 2, 3, 4, and 6 hours after dosing on day 15 of cycle 1, and random samples were collected on day 1 of cycles 3 and 5.

Assay Method

Plasma concentrations of pexidartinib and ZAAD were determined separately by liquid chromatography–tandem mass spectrometry methods developed and validated at Celerion (Lincoln, Nebraska). Plasma samples containing the analytes and stable-labeled internal standard ($^{13}C,d_5$-pexidartinib) were extracted using the protein precipitation procedure.

For pexidartinib, extracted samples were analyzed on a Zorbax Bonus-RP column (50 mm length, 2.1 mm internal diameter, 3.5 μm particle size; Agilent Technologies, Santa Clara, California) with a mobile phase of 30:5:65:0.05 (v/v/v/v) acetonitrile:methanol:5 mM ammonium formate:heptafluorobutyric acid, at a flow rate of 0.5 mL/min. Detection was performed on an AB SCIEX API 4000 triple quadrupole mass spectrometer (Sciex, Framingham, Massachusetts) with an electrospray ionization source, and multiple reaction monitoring of m/z 418.1 $\rightarrow$ 258.3 for pexidartinib and m/z 424.2 $\rightarrow$ 263.3 for internal standard. The within-run and between-run assay precision was 0.8% to 7.2% and 3.3% to 6.3%, respectively, for quality control samples at concentrations of 10 to 3750 ng/mL, and the accuracy ranged from 92.3% to 107.0%, respectively. The lower limit of quantification was 10 ng/mL for pexidartinib.

For ZAAD, extracted samples were analyzed on an ACE C18 column (50 mm length, 2.1 mm internal diameter, 5 μm particle size; Advanced Chromatography Technologies, Aberdeen, Scotland) with a mobile phase of 5:95:1 (v/v/v) acetonitrile:water:formic acid, at a flow rate of 0.6 mL/min. ZAAD-1006a and internal standard were detected on an AB SCIEX API 4000 triple quadrupole mass spectrometer (Sciex, Framingham, Massachusetts) using an electrospray ionization source, and multiple reaction monitoring of m/z 594.2 $\rightarrow$ 418.1 (ZAAD) and m/z 424.2 $\rightarrow$ 263.3 (internal standard). The within-run and between-run assay precision was 1.5% to 11.4%, and 7.2% to 11.8%, respectively, for quality control samples at concentrations of 10 to 3750 ng/mL, and the accuracy ranged from 95.9% to 117%. The lower limit of quantification was 10 ng/mL for ZAAD.

Population PK Analysis

Population PK analyses were conducted via nonlinear mixed-effects modeling using NONMEM software, Version 7.3 (ICON Development Solutions, Hanover, Maryland). The first-order conditional estimation with interaction method was employed for all model runs. Data analysis language, R (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria), was used for pre- and postprocessing of model input and output files.

Population PK Model of Pexidartinib

The structural PK model was a 2-compartment model with sequential zero- and first-order absorption and lag time, and linear elimination from the central compartment. Interindividual variability (IIV) was included on clearance from the central compartment (CL/F), central volume of distribution (Vc/F), peripheral volume of distribution (Vp/F), intercompartmental clearance (Q/F), and absorption rate constant (KA). Interoccasion variability (IOV) was added to KA and relative bioavailability (F1). Both IIV and IOV were modeled using exponential terms. In addition, a proportional error model was used to describe the residual variability.

The following covariates were evaluated to assess their impact on absorption and/or disposition parameters using a full-model approach[5]: subject demographics (age, sex, body weight [WT], and race); liver and renal function parameters (aspartate aminotransferase [AST], alanine aminotransferase, total bilirubin [TBIL], and creatinine clearance [CRCL] calculated by the Cockcroft-Gault equation[6]); drug formulation (phase 1 vs phase 3 formulation); and study population (healthy subjects vs patients). The full-model approach emphasizes parameter estimation rather than stepwise hypothesis testing. Covariates in the full model are chosen based on biological plausibility and clinical interest. Briefly, all covariates were added to create a full model, then inference was made about the covariate effects. Following the full-model estimation, any remaining covariates were evaluated graphically to assess if any trends remained.

The performance of the final full-model was assessed by goodness-of-fit criteria and visual predictive check (VPC). Goodness-of-fit criteria included diagnostic scatter plots, convergence with $\geq$3 significant digits, plausibility of parameter estimates, precision of parameter estimates, correlation between model parameter estimation errors $<$0.95, and the Akaike information criterion. A VPC was performed, which is similar to the posterior predictive check[7] but assumes that parameter uncertainty is negligible relative to interindividual and residual variance. To account for different pexidartinib doses used in healthy-subject studies, the simulated and observed concentrations were normalized by dose to generate the VPC plots. VPC plots for patients were not dose normalized.

Population PK Model of ZAAD. Observed plasma concentrations of ZAAD were analyzed separately using a similar structure model as that for pexidartinib. The fraction of ZAAD formation was fixed to 0.38 based on the results of a mass-balance study of pexidartinib in healthy subjects (data on file, Daiichi Sankyo, Inc.). This was treated as F1 in the model, which represented the fraction of pexidartinib dose going through

glucuronidation to form the metabolite ZAAD. Covariates evaluated in the ZAAD full model were generally similar to those in the pexidartinib model, except there were no Asian subjects or phase 1 formulation in the ZAAD analysis data set; thus, effects of race (Asian vs non-Asian) and drug formulation (phase 1 vs phase 3 formulation) were not included in the ZAAD model. Study U121 included much higher pexidartinib doses than the other studies. Population prediction was shown to be generally overpredicted compared to the observed data in study U121. As a result, an effect of high dose on F1 was also considered in the ZAAD full model to improve the population prediction.

Evaluation of Covariate Effects on Pexidartinib and ZAAD Exposures. The impact of covariates on the steady-state exposures (steady-state area under the curve values from 0 to 24 hours [$AUC_{0\text{-}24,ss}$] and steady-state maximum concentration [$C_{max,ss}$]) of pexidartinib and ZAAD were evaluated by both univariate and multivariate approaches. For the univariate approach, simulations were performed by varying each covariate value one at a time and keeping other covariates as constant (ie, categorical covariates were set at the reference categories, and continuous covariate values were set to the median or reference values in the data set), assuming a dose regimen of 400 mg twice daily with phase 3 formulation. A total of 500 simulations were conducted for each covariate effect using virtual subjects with specified covariate attributes, taking into account the uncertainty in the fixed-effect model parameters (covariate parameter estimates were sampled from the point estimate and parameter estimation uncertainty). Steady-state exposures of pexidartinib and ZAAD ($AUC_{0\text{-}24,ss}$ and $C_{max,ss}$) were derived at the 5th, 25th, 75th, and 95th percentiles of the continuous covariates, or at each level of the categorical covariates, and then compared to that for a typical patient (with reference covariate values) via a forest plot. For the multivariate approach, individual pexidartinib exposures were predicted from the individual post hoc PK parameters and then summarized and compared among subgroups of patients who had normal renal function (CRCL ≥90 mL/min), mild (CRCL 60-89 mL/min) or moderate (CRCL 30-59 mL/min) renal impairment,[8] or subgroups of patients with normal hepatic function or mild hepatic impairment according to the National Cancer Institute Organ Dysfunction Working Group classification.[9]

Results

Data

The final data set for population PK modeling of pexidartinib included 159 healthy subjects contributing 6250 measurable (ie, not below the limit of quantification) pexidartinib concentrations and a total of 216 patients with TGCT or other solid tumors contributing 2180 measurable pexidartinib concentrations (Table 1). The pooled population was predominantly male (62%) with a mean WT of 79.7 kg (range, 31.8-154 kg) and a mean age of 45.5 years (range 18-84 years). The races of the study population were White (72%), Black (22%), Asian (2%), Native Hawaiian or other Pacific Islander (1%), American Indian/Alaskan Native (1%), and other (2%) (Table 2). The final data set for ZAAD population PK modeling included 93 healthy subjects contributing 2693 measurable ZAAD concentrations and a total of 84 patients with TGCT or other solid tumors contributing 453 measurable ZAAD concentrations.

Population PK Model of Pexidartinib

The observed concentration-time profiles of pexidartinib after a single oral administration to healthy subjects are illustrated in Figure 1A according to study and dose. These profiles indicate that pexidartinib exposure was generally dose proportional over the dose ranges evaluated (200-2400 mg). After reaching peak plasma concentrations, pexidartinib concentrations exhibited a bi-exponential decay. Steady-state plasma concentration–time curves of pexidartinib in studies involving patients with TGCT or other solid tumors (ie, PLX108-01 and ENLIVEN) are illustrated in Figure 1B. These curves indicate that plasma concentrations of pexidartinib were maintained over time following multiple doses.

In the final full model, the effects of WT, sex, race (Asian vs non-Asian), CRCL, AST, and TBIL and study population (healthy subjects vs patients) on CL/F are shown in the following equation. AST and TBIL were tested as time-varying variables, while all other variables were tested using their baseline values.

$$CL/F_{i,} = exp(\theta_1) \bullet (WT_i/80)^{0.75} \bullet CRCL_i \bullet ASCL_i \bullet ASTCL_{i,t} \bullet TBILCL_{i,t} \bullet HSTUDYCL_i \bullet SEXCL_i \bullet \exp(\eta_{CL/F,i})$$

where:

- $CRCL_i = 1$ for subjects with baseline $CRCL_i \geq 90$, and $CRCL_i = (\mathrm{CRCL}_i/90)^{\theta 9}$ for subjects with baseline $\mathrm{CRCL}_i < 90$
- $ASCL_i = 1$ for non-Asian subjects, and $ASCL_i = \exp(\theta_{10})$ for Asian subjects
- $ASTCL_i = 1$ for subjects with $AST_i \leq 80$, and $ASTCL_{i,t} = (AST_i/80)^{\theta 11}$ for subjects with $AST_i > 80$
- $TBILCL_i = 1$ for subjects with $TBIL_i \leq 20.5$, and $TBILCL_i = (TBIL_i/20.5)^{\theta 12}$ for subjects with $TBIL_i > 20.5$

Table 2. Summary of Subject Demographic and Baseline Characteristics

Characteristic	Healthy Subjects (n = 159)	Patients (n = 216)	Total (N = 375)
Age, y, median (range)	38 (18-60)	50 (20-84)	44.0 (18-84)
Sex, n (%)			
Male	130 (82)	101 (47)	231 (62)
Female	29 (18)	115 (53)	144 (38)
Race, n (%)			
Caucasian	72 (45)	197 (91)	269 (72)
Black or African American	77 (48)	7 (3)	84 (22)
Asian	3 (2)	5 (2)	8 (2)
American Indian or Alaska Native	1 (1)	2 (1)	3 (1)
Native Hawaiian or other Pacific Islander	1 (1)	3 (0)	4 (1)
Other	5 (3)	2 (0)	7 (2)
Weight, kg, median (range)	79.3 (50.9-106.8)	79.6 (31.8-154.2)	79.3 (31.8-154.2)
Liver function variables, median (range)			
ALT, U/L	17.0 (9.0-38.0)	18.0 (6.0-101.0)	18.0 (6.0-101.0)
AST, U/L	19.0 (12.0-40.0)	19.0 (10.0-188.0)	19.0 (10.0-188.0)
TBIL, mg/dL	8.6 (1.7-20.5)	6.8 (1.7-31.0)	6.8 (1.7-31.0)
CRCL, mL/min, median (range)	114.0 (76.4-150.0)	113.0 (44.3-150.0)	113.0 (44.3-150.0)
Formulation, n (%)			
Phase 3 formulation	144 (91)	84 (39)	228 (61)
Phase 1 formulation	15 (9)	132 (61)	147 (39)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRCL, creatinine clearance (mL/min); TBIL, total bilirubin (μmol/L).

- $HSTUDYCL_i = 1$ for patients, and $HSTUDYCL_i = \exp(\theta_{13})$ for healthy subjects
- $SEXCL_i = 1$ for males, and $SEXCL_i = \exp(\theta_{14})$ for females

The effect of WT on Vc/F, Vp/F, and Q/F was assessed, respectively, in the following equations:

$$Vc/F_i = \exp(\theta_2) \bullet (WT_i/80) \bullet \exp(\eta_{Vc/F,i})$$

$$Vp/F_i = \exp(\theta_3) \bullet (WT_i/80) \bullet \exp(\eta_{Vp/F,i})$$

$$Q/F_i = \exp(\theta_4) \bullet (WT_i/80)^{0.75} \bullet \exp(\eta_{Q/F,i})$$

The first-order absorption rate constant (KA) was defined by:

$$KA_i = \exp(\theta_5) \bullet \exp(\eta_{KA,i} + \eta_{KA,iov})$$

Absorption lag time ($ALAG1_i$) was defined by:

$$ALAG1_i = \exp(\theta_6)$$

The zero-order absorption duration (D1) was defined by:

$$D1_i = \exp(\theta_7)$$

The F1 was defined by:

$F1_i = 1 \bullet \exp(\eta_{F1,iov})$ for phase 3 formulation

$F1_i = 1 \bullet \exp(\theta_8) \bullet \exp(\eta_{F1ph1,i} + \eta_{F1,iov})$ for phase 1 formulation

The phase 3 formulation was observed to have 17% higher exposure than the phase 1 formulation based on a dedicated relative bioavailability study (data on file, Daiichi Sankyo, Inc.). Therefore, a formulation effect on F1 of the phase 1 formulation to the phase 3 formulation was fixed to 0.855 in the model, that is, $\exp(\theta_8) = 0.855$.

Interindividual random-effect distributions were modeled using exponential variance models, with a full block covariance between CL/F, Vc/F, and Vp/F. Only diagonal elements were estimated for IIVs for Q/F, KA, and F1. In addition, IOV on KA and F1 were added to the model to account for the observed large variability in the absorption phase.

Parameter estimates from the final population PK model for pexidartinib are summarized in Table 3. Based on this model, pexidartinib CL/F was estimated to be 5.83 L/h in a typical male non-Asian patient with a WT of 80 kg, CRCL $\geq$90 mL/min, AST $\leq$80 U/L, and TBIL $\leq$20.5 μmol/L. Model-estimated pexidartinib CL/F in a typical female non-Asian patient is 5.07 L/h, reflecting a 13% lower CL/F in women (Table 3). All model structural parameters were estimated with good precision and narrow 95% confidence intervals (CIs). Variance parameter estimates suggested a moderate to high degree of IIV with percent coefficient of variation

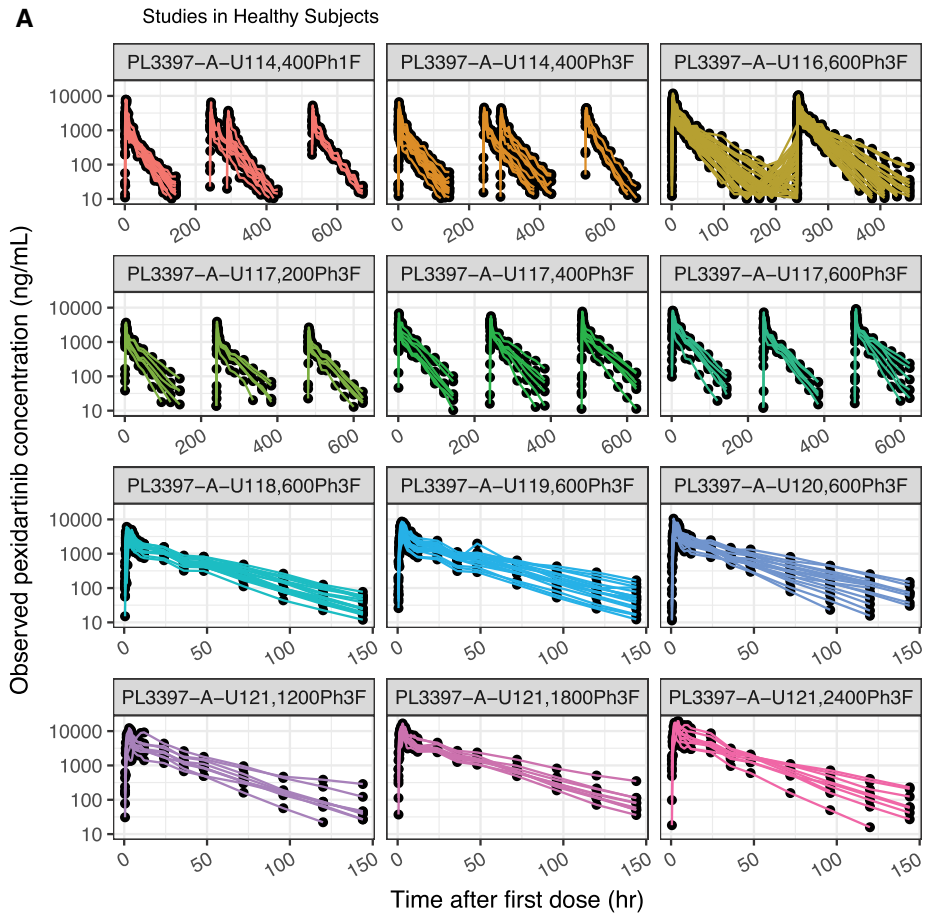

Figure 1. Observed pexidartinib concentrations vs time after first dose in healthy subjects following oral doses of 200 mg to 2400 mg (A) and in patients from studies PLX108-01 and ENLIVEN (B). Number before Ph refers to dose level (mg). Ph1F, phase 1 formulation; Ph3F, phase 3 formulation.

of 30% for CL/F, 56.1% for Vc/F, 48.8% for Vp/F, 70.8% for Q/F, 165% for KA, and 25.9% for F1. IOV was high for KA (229%) and moderate for F1 (32.6%). Shrinkage estimates of interindividual random effects were 22.8%, 27.8%, 33.7%, 37%, 48.7%, and 37.1%, respectively, for CL/F, Vc/F, Vp/F, Q/F, KA, and F1. Shrinkages for interoccasion random effects were high for KA (ranging from 48.7% to 69.2%) and F1 (ranging from 26.6% to 62.9%), due to the relatively small number of samples at each occasion. Proportional residual variance estimates were modest for studies in patients (29.7%) and for studies in healthy subjects (19.6%), and the corresponding shrinkages were 14.7% and 6.85%, respectively.

Remaining trends in covariates were evaluated graphically based on the full model results. As shown in Figure S1, no additional covariate effects, such as sex and Black race, were demonstrated. In addition, a second full model was estimated where the AST and TBIL effects were estimated without a cutoff value. These results were similar to the original full model with power exponents demonstrating an even smaller effect of AST and TBIL on CL (data on file, Daiichi Sankyo, Inc.). The condition number, calculated using the largest eigenvalue divided by the smallest eigenvalue in NONMEM output, was 53.4, supporting reasonable stability of the model.

Dose-normalized VPCs, stratified by study population (healthy subjects vs patients) and formulation (phase 1 formulation vs phase 3 formulation) were presented in Figure 2. Results demonstrated overall reasonable agreement between the observed and simulated pexidartinib concentrations in healthy subjects and patients. Goodness-of-fit plots also suggested that the final model described the observed data well (Figure S2). These results together supported that the final model was suitable for simulations.

Population PK Model of ZAAD

Similar to pexidartinib, ZAAD concentrations showed a biexponential decay (Figure S3A), and steady-state concentrations were maintained over time (Figure S3B). Parameter estimates from the final population PK model for ZAAD are summarized in Table S1. Dose-normalized VPCs for healthy subjects and normal VPCs for patients (Figure S4) and

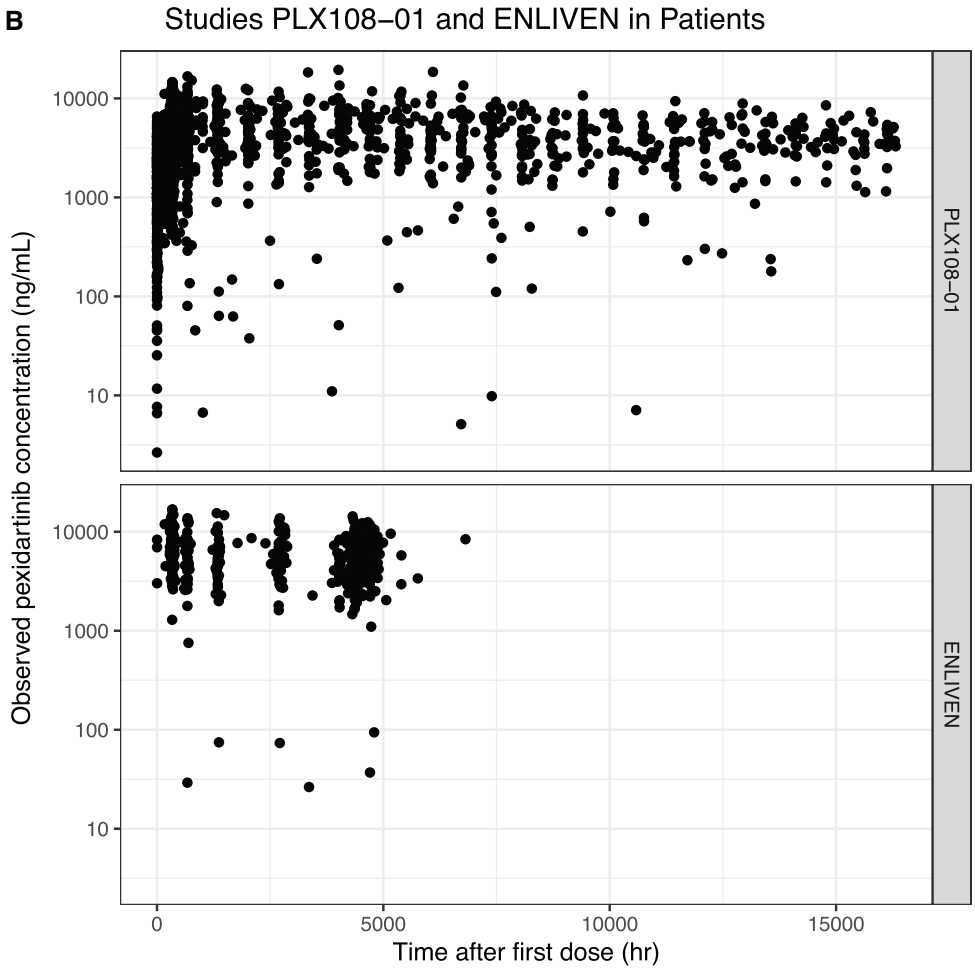

Figure 1. *Continued*

goodness-of-fit plots (Figure S5) also confirmed that the final model described the observed data and was suitable for simulation.

Model Applications

Covariate Effects on Pexidartinib Exposure

Demographic variables (ie, age, sex, WT, race), laboratory values (ie, AST, TBIL, CRCL), drug formulation (ie, phase 1 vs phase 3 formulation), and study populations (healthy subjects vs patients with tumors) were included as covariates in the final full model of pexidartinib. Their effects on pexidartinib exposure, as assessed by $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$, are shown in a forest plot in Figure 3. Asians had a 21% lower $AUC_{0\text{-}24,ss}$ compared to non-Asians, but there was a wide 95%CI. Similarly, healthy subjects had a 21% lower $AUC_{0\text{-}24,ss}$ compared with patients with TGCT or other solid tumors, with the 95%CI falling partially outside the 80% to 125% range. All other covariates (sex, CRCL, AST, TBIL) showed a <20% effect on pexidartinib exposure, except WT, for which a low value of 53 kg (5th percentile) resulted in an approximately 36% increase in $AUC_{0\text{-}24,ss}$ compared with the median value of 80 kg.

Covariate effects on $C_{max,ss}$ were generally similar to those on $AUC_{0\text{-}24,ss}$ for pexidartinib. The only covariates that showed a >20% effect on pexidartinib $C_{max,ss}$ were WT of 53 kg (5th percentile), which was associated with a 40% increase in $C_{max,ss}$, and WT of 108 kg (95th percentile), which was associated with a 21% decrease in $C_{max,ss}$.

Model-predicted pexidartinib exposure from pexidartinib 400 mg twice daily to patients in the PLX108-10 and ENLIVEN studies, stratified by tumor type and renal or hepatic function, is presented in Figure 4. Patients with mild renal impairment had approximately 23% higher (TGCT patients, n = 21) or 17% higher (non-TGCT patients, n = 30) $AUC_{0\text{-}24,ss}$ compared with the corresponding patient groups with normal renal function (TGCT patients, n = 101; non-TGCT patients, n = 55). There was only 1 patient with TGCT and 8 patients without TGCT who had moderate renal impairment. This limited number does not allow meaningful interpretation (Figure 4A). Pexidartinib $AUC_{0\text{-}24,ss}$

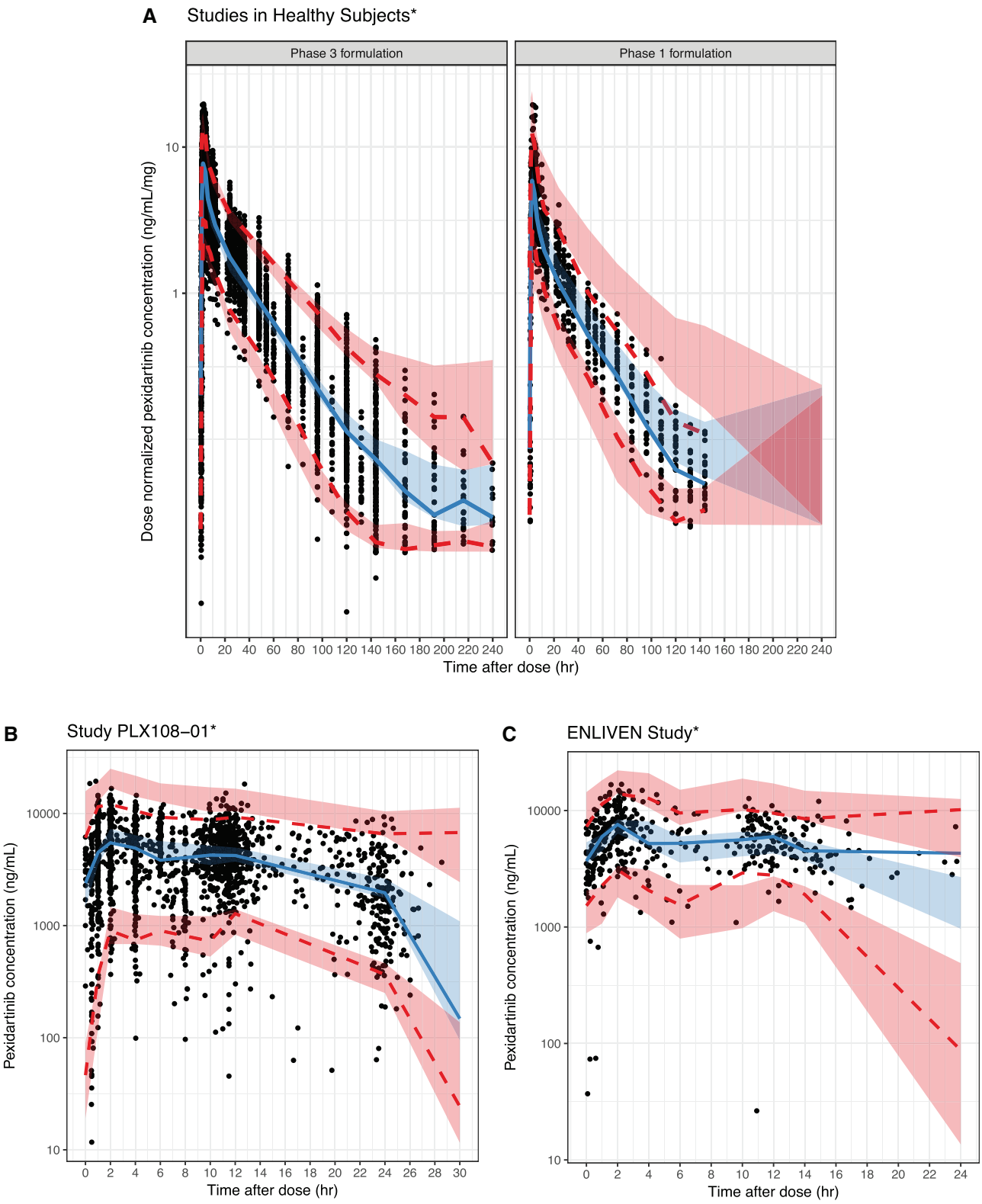

Figure 2. Dose normalized visual predictive check plots of pexidartinib concentrations for studies in healthy subjects (A), study PLX108-01 (B), and the ENLIVEN study (C). *Visual predictive check plot for studies in healthy subjects were stratified by phase 1 formulation and phase 3 formulation, because both formulations were used in these studies. Study PLX108-01 used phase 1 formulation, and ENLIVEN study used phase 3 formulation.

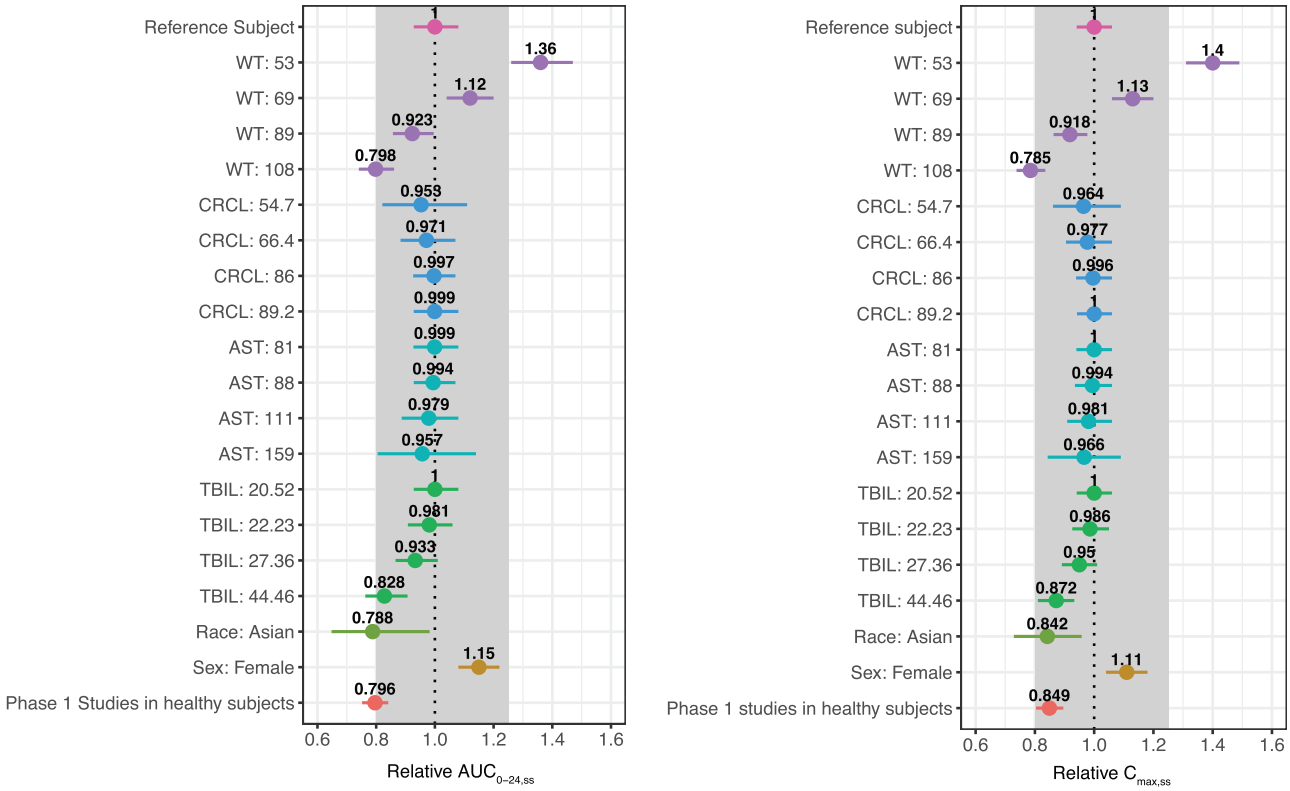

Figure 3. Plot of covariate effects on pexidartinib $AUC_{0\text{-}24,ss}$ (A) and $C_{max,ss}$ (B) $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$ were derived based on a dose regimen of 400 mg twice daily with phase 3 formulation. $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$ relative to the typical subject with reference covariates (male, patient, WT of 80 kg, non-Asian, CRCL ≥90 mL/min, AST ≤80 U/L, and TBIL ≤20.5 μmol/L) are plotted by representative covariate value. The representative values of WT, CRCL, AST, and TBIL were the 5th, 25th, 75th, and 95th percentiles of the observed individual WT, the observed individual CRCL <90 mL/min, the observed AST >80 U/L, and the observed TBIL >20.5 μmol/L, respectively. Dot represents the median, and solid horizontal line represents the 95%CI of relative $AUC_{0\text{-}24,ss}$ or $C_{max,ss}$ at that covariate value. The gray shaded region represents covariate effect within a range of 80% to 125%. AST, aspartate aminotransferase (U/L); $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration–time curve from time 0 to 24 hours; $C_{max,ss}$, steady-state maximum plasma concentration; CRCL, creatinine clearance (mL/min); TBIL, total bilirubin (μmol/L); WT, body weight (kg).

appears to be similar in patients with normal hepatic function and patients with mild hepatic impairment, regardless of tumor type (Figure 4B).

Covariate Effects on ZAAD Exposure

Figure S6 shows the forest plot of relative changes in ZAAD exposure by covariates. $AUC_{0\text{-}24,ss}$ increased with decreasing WT and increasing AST, while CRCL and TBIL had minimal impact. At extreme WT and AST values, $AUC_{0\text{-}24,ss}$ values fell outside the range of 80% to 125%, with a 29% higher $AUC_{0\text{-}24,ss}$ at a WT value of 57 kg (5th percentile), a 21% lower $AUC_{0\text{-}24,ss}$ at a WT value of 109 kg (95th percentile), and a 76% higher $AUC_{0\text{-}24,ss}$ at an AST value of 188 U/L (95th percentile of observed AST value in ZAAD data set) (Figure S6A). Healthy subjects appeared to have approximately 22% lower $AUC_{0\text{-}24,ss}$ compared to patients with TGCT, while women had 20% higher $AUC_{0\text{-}24,ss}$ than men. Covariate effects on $C_{max,ss}$ values for ZAAD were similar to those on $AUC_{0\text{-}24,ss}$ (Figure S6B).

Additional Simulations

Based on the established population PK models for pexidartinib and ZAAD, additional simulations were conducted to obtain individual $AUC_{0\text{-}12,ss}$ and $C_{max,ss}$ values for the dosage regimen of 400 mg twice daily in the ENLIVEN study. The simulation assumed all patients received pexidartinib 400 mg twice daily for 4 weeks. Results are summarized in Table 4. Exposure increased for both pexidartinib and ZAAD over time, with mean accumulation ratios of 3.6 and 4.6, respectively. The metabolite-to-parent ratio, adjusted by molecular weight, was 1.25 as measured by $AUC_{0\text{-}12,ss}$.

Discussion

TGCT is a rare, locally aggressive neoplasm of the joint or tendon sheath.[10] There is a wide age distribution at diagnosis of TGCT,[4,11] and some data suggest that TGCT is more common in women than in men.[4,11] In order to make appropriate dose recommendations in different patient populations or subgroups, it is

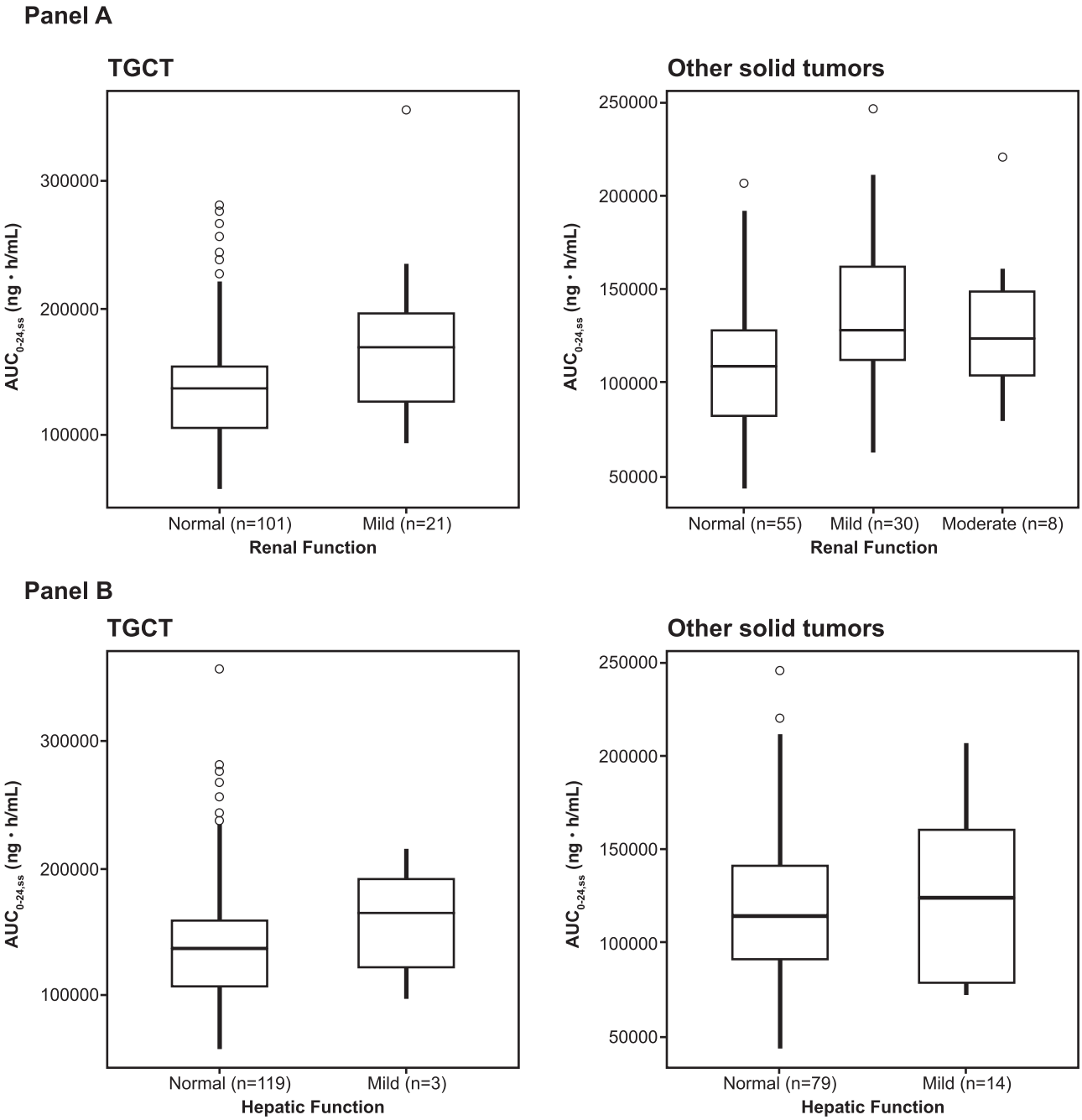

Figure 4. Predicted pexidartinib steady-state exposure ($AUC_{0\text{-}24,ss}$) by renal function (A) and hepatic function (B). $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration–time curve from time 0 to 24 hours; TGCT, tenosynovial giant cell tumor.

important to understand the PK profiles of pexidartinib and its metabolite ZAAD and to determine whether covariates, such as demographic and clinical factors, affect their PK and contribute to the IIVs. This is a first analysis to characterize population PK characteristics of pexidartinib and ZAAD in healthy subjects and patients with TGCT, with the ultimate goal to support pexidartinib labeling and dosing in subgroups of patients of interest, taking into account the results of this analysis and the known exposure-response relationships for pexidartinib.

The structural PK model for pexidartinib was a 2-compartment model with sequential zero- and first-order absorption and lag time and linear elimination from the central compartment. A full covariate modeling approach was used to assess variables that are of clinical interest and/or biologically relevant. This full-model approach is considered the most parsimonious

Table 3. Pexidartinib Model Pharmacokinetic Parameter Estimates

Parameter	Estimate[a]	95%CI[b]
CL/F ($\exp(\theta_1)$) (WT/80)$^{0.75}$	5.83 L/h	5.43 to 6.27
(CRCL$_{<90}$/90)$^{\theta 8}$	−0.0941	−0.402 to 0.214
(Asian)•$\exp(\theta_{10})$	1.27	1.05 to 1.54
(AST$_{>80}$/80)$^{\theta_{11}}$	0.0709	−0.180 to 0.322
(TBIL$_{>20.5}$/20.5)$^{\theta_{12}}$	0.244	0.183 to 0.306
(StHT)•$\exp(\theta_{13})$	1.26	1.16 to 1.36
(Female)•$\exp(\theta_{14})$	0.869	0.808 to 0.934
V_c/F($\exp(\theta_2)$) (WT/80)	98.0 L	90.0 to 107
V_p/F($\exp(\theta_3)$) (WT/80)	116 L	106 to 128
Q/F($\exp(\theta_4)$) (WT/80)$^{0.75}$	20.7 L/h	17.9 to 23.8
KA($\exp(\theta_5)$)	6.82 h^{-1}	5.09 to 9.14
ALAG1($\exp(\theta_6)$)	0.387 h	0.385 to 0.390
D1($\exp(\theta_7)$)	1.22 h	1.20 to 1.25
F1$_{Phase1}$($\exp(\theta_8)$)	0.855 Fixed	
$\Omega_{1.1}$ CL/F	0.0860 (%CV = 30)	0.0633 to 0.109
$\Omega_{2.1}$ COV$_{Vc/F-CL/F}$	0.0774 (corr = 0.504)	0.0425 to 0.112
$\Omega_{2.2}$ Vc/F	0.274 (%CV = 56.1)	0.207 to 0.341
$\Omega_{3.1}$ COV$_{Vp/F-CL/F}$	0.0149 (corr = 0.110)	−0.0178 to 0.0476
$\Omega_{3.2}$ COV$_{Vp/F-Vc/F}$	−0.0467 (corr = −0.193)	−0.105 to 0.0111
$\Omega_{3.3}$ V_p/F	0.213 (%CV = 48.8)	0.152 to 0.275
$\Omega_{4.4}$ Q/F	0.406 (%CV = 70.8)	0.271 to 0.541
$\Omega_{5.5}$ KA	1.31 (%CV = 165)	0.648 to 1.98
$\Omega_{6.6}$Ph1Form	0.101 (%CV = 32.6)	0.0592 to 0.143
$\Omega_{7.7}$ IOV KA($\eta_{7\text{-}11}$)	1.83 (%CV = 229)	1.26 to 2.40
$\Omega_{12.12}$ IOV F1($\eta_{12\text{-}21}$)	0.0652 (%CV = 25.9)	0.0560 to 0.0743
$\Sigma_{1.1,prop,pat}$(ε_1)	0.0883 (%CV = 29.7)	0.0839 to 0.0927
$\Sigma_{2.2,prop,ht}$(ε_2)	0.0384 (%CV = 19.6)	0.0377 to 0.0391

Ω, interindividual covariance matrix; $\Sigma_{1.1,prop,pat}$, proportional residual variability for studies in patients; $\Sigma_{2.2,prop,ht}$, proportional residual variability for phase 1 studies in healthy subjects; $\Omega_{6.6}$ph1Form, interindividual variability of F1 for the phase 1 formulation; ALAG$_1$, lag time; AST, aspartate aminotransferase (U/L); CI, confidence interval; CL/F, apparent clearance; corr, correlation; CRCL, creatinine clearance (mL/min); CV, coefficient of variation; D1, duration of zero-order deposition; F1, relative bioavailability of phase 1 formulation to phase 3 formulation; IOV, interoccasion variability (variance); KA, first-order absorption rate constant; Q/F, apparent intercompartmental clearance; StHT, phase 1 studies in healthy subjects; TBIL, total bilirubin (μmol/L); V_c/F, apparent central compartment volume; V_p/F, apparent peripheral compartment volume; WT, body weight (kg); θ, fixed effect parameter.

[a] Estimates of θ modeled in the log domain were exponentiated and are reported in the table.

[b] 95%CI was derived from standard error obtained from the NONMEM $COVARIANCE step.

Table 4. Summary of Predicted Pexidartinib and ZAAD Exposures From the ENLIVEN Trial After Pexidartinib 400 mg Twice Daily for 4 Weeks

Parameter, Mean (SD)	Pexidartinib	ZAAD
$AUC_{0\text{-}12}$ on day 1, ng • h/mL	21 529 (5231)	30 602 (12 871)
$AUC_{0\text{-}12}$ at steady state, ng • h/mL	77 465 (24 975)	137 872 (62 005)
C_{max} on day 1, ng/mL	3524 (1093)	4194 (2182)
C_{max} at steady state, ng/mL	8625 (2746)	13 564 (6095)
Accumulation ratio[a]	3.6 (0.8)	4.6 (0.8)
CL/F, L/h	5.6 (1.6)	1.8 (0.4)

$AUC_{0\text{-}12}$, area under the plasma concentration–time curve from time 0 to 12 hours; C_{max}, maximum plasma concentration; CL/F, apparent clearance; SD, standard deviation.

[a] Calculated as $AUC_{0\text{-}12}$ at steady state divided by $AUC_{0\text{-}12}$ on day 1.

and can avoid potential bias in estimates compared to the stepwise forward addition process, and therefore has been adopted in population PK modeling to make inferences about the covariate effects. [5,12–14] As demonstrated by the residual-based goodness-of-fit plots as well as simulation-based visual predictive check, the final full model adequately described pexidartinib PK profiles in healthy subjects and patients with TGCT and other solid tumors. Model-estimated CL/F of pexidartinib was 5.83 L/h for a typical subject with the reference covariates (male, non-Asian patient with a WT of 80 kg, CRCL ≥90 mL/min, AST ≤80 U/L, and TBIL ≤20.5 μmol/L). The analysis showed that the estimated exposure values for patients receiving pexidartinib 400 mg twice daily increased following multiple daily dosing, with accumulation ratios of 3.6 and 4.6 for pexidartinib and ZAAD, respectively. These results are in line with published phase 1 results evaluating pexidartinib in predominantly White patients[15] and Asian patients[16] with solid tumors.

In the assessment of the effect of covariates on pexidartinib, small effect of study population was noted, with healthy subjects having 26% higher CL/F and 21% lower $AUC_{0\text{-}24,ss}$ compared to patients with TGCT. This is possibly due to differences between the 2 populations or study type that were not accounted for in the population PK model (ie, other than the demographic and clinical covariates that were already included in the model). It could also be related to the difference in study condition. PK data in healthy subjects were collected in the strictly controlled fasted condition (ie, after an overnight fast of at least 10 hours, with only water allowed for 4 hours after dosing). Even though patient studies had specified dosing instructions to take pexidartinib either 1 hour before or 2 hours after eating, compliance with the prescribed dosing condition cannot be confirmed in studies conducted in an outpatient setting. Because pexidartinib shows a positive food effect,[3] the observed slightly higher pexidartinib exposure in patients could be due to the differences in stomach contents between healthy subject studies conducted after an overnight fast vs patient studies with twice-daily dosing (where some food could still be present in the stomach). Regardless of the exact reasons, such an observation has little impact on the overall understanding of the clinical pharmacology of pexidartinib and is not expected to have any meaningful clinical implications.

In this analysis, Asian race has an approximately 21% lower exposure to pexidartinib, as assessed by

$AUC_{0\text{-}24,ss}$. The corresponding 95%CI fell partially outside the 80% to 125% range, but it is also very wide due to the low number of Asians included (n = 8). This aspect deserves to be further investigated when more data in Asian patients are available. Patient WT and sex had no clinically meaningful effect on pexidartinib exposure, with the exception of a low value of 53 kg for WT resulting in an approximately 36% increase in $AUC_{0\text{-}24,ss}$ compared with the median value of 80 kg. Hepatic function parameters, such as AST and TBIL, had a minimal effect on pexidartinib PK. Comparison of patients with normal hepatic function or mild hepatic impairment also showed the similar findings. The lack of a clinically meaningful effect on pexidartinib PK suggests that no dose adjustment is recommend for the patient characteristics as described above.

A significant effect of renal function on pexidartinib PK was not suggested by the current analysis; however, the data set included a relatively narrow range of CRCL values and a small proportion of subjects with renal impairment. Thus, the evaluation of the effect of CRCL in this population PK analysis was limited. A previous dedicated study designed to assess the effect of renal impairment on the PK of pexidartinib found that some of the individual categories of renal impairment (ie, mild, moderate, and severe renal impairment groups) showed an approximately 30% increase in pexidartinib AUC. Comparison of post hoc individual pexidartinib exposure from this analysis suggested that TGCT patients with mild renal impairment had approximately 23% higher $AUC_{0\text{-}24,ss}$ compared with those with normal renal function. Given these results, the product labeling recommends a dose reduction (200 mg in the morning and 400 mg in the evening) for those with mild to severe renal impairment (ie, CRCL $\leq$60 mL/min).[2]

Pexidartinib is extensively metabolized, with ZAAD being identified clinically as the sole major metabolite. ZAAD is minimally active pharmacologically, but its systemic exposure has been shown to be higher than that of pexidartinib. In this analysis, we also evaluated the population PK characteristics of ZAAD, based on a subset of data collected from healthy subjects and patients with TGCT. The analysis of ZAAD was performed as a fit for purpose exercise to determine individual ZAAD exposures (C_{max} and AUC) for a subsequent exposure-safety analysis (not discussed in this article). Given that a sequential approach was used rather than a simultaneous approach for parent-metabolite modeling. Overall, the developed model was able to provide a reasonable description of the observed concentration-time profiles of ZAAD in both healthy subjects and patients with TGCT. Covariate assessment suggested that the effects of covariates on ZAAD exposure were similar to those on pexidartinib, with small and clinically nonmeaningful effects observed.

Conclusion

The population PK of pexidartinib and ZAAD in healthy subjects and patients with solid tumors (including TGCT) are well characterized by a 2-compartment model with sequential zero- and first-order absorption with a lag time and linear elimination. The results also indicate small and generally clinically unmeaningful effects of patient characteristics on pexidartinib and ZAAD PK profiles. Therefore, with the exception of renal impairment, no dose adjustment is recommended according to the patient's body weight, sex, or race or in patients with mild hepatic impairment.

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Conflicts of Interest

O.Y. reports employment with Daiichi Sankyo. A.J.W. reports grants to his institution from Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Plexxikon, Karyopharm Therapeutics, AADi Inc., and Celldex; he served as a consultant for Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Loxo, and Novartis. J.K. reports personal fees for consulting from Daiichi Sankyo during the conduct of the study. W.K. reports personal fees for consulting from Daiichi Sankyo during the conduct of the study. H.Z. reports employment with Daiichi Sankyo. M.v.d.S. reports grants to his institution from Daiichi Sankyo during the conduct of the study. W.D.T. reports a standard budget for site participation in the clinical trial from Daiichi Sankyo during the conduct of the study; personal fees for advisory board and consulting from Eli Lilly, EMD Serono, Eisai, Janssen, Immune Design, Daiichi Sankyo, Blueprint, Loxo, GlaxoSmithKline, Novartis, Adaptimmune, and Agios Pharmaceuticals outside the submitted work; personal fees for advisory board from NanoCarrier and Deciphera outside the submitted work; a patent Companion Diagnostic for CDK4 inhibitors - 14/854,329 pending to MSKCC/SKI; participation on the Scientific Advisory Board for Certis Oncology Solutions and Atropos Therapeutics; stock ownership with Certis Oncology Solutions and Atropos Therapeutics; and served as a consultant for Daiichi Sanyko for FDA ODAC Meeting Pexidartinib. H.G. reports research compensation to his institution from Daiichi Sankyo. J.H.H. reports personal fees for consulting from Daiichi Sankyo outside the submitted work. D.S. reports employment with and stock ownership in Daiichi Sankyo. S.S. reports personal fees for consulting from Bayer, Bavarian Nordic, Deciphera, Eli Lilly, Epizyme Inc., Daiichi Sankyo, Karyopharm, Immune Design, Intellisphere, Maxivax, PharmaMar, and Takeda outside the submitted work; research funding to her institution from Amgen Dompé, Advenchen, Bayer, Bavarian Nordic, Blueprint, Deciphera, Eli Lilly, Epizyme Inc., Daiichi Sankyo,

Karyopharm, Novartis, Pfizer, and PharmaMar outside the submitted work; travel coverage from PharmaMar outside the submitted work; and honoraria from Eli Lilly and PharmaMar outside the submitted work. No other conflicts of interest were reported.

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Data Sharing

Deidentified individual participant data and applicable supporting clinical trial documents may be available upon request at https://www.clinicalstudydatarequest.com//. In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo, Inc., will continue to protect the privacy of our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found at https://www.clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-DS.aspx.

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Supplemental Information

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