Poster M-028

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

Ophelia Yin,[1] Jia Kang,[2] William Knebel,[2] Hamim Zahir,[1] Michiel van de Sande,[3] William D. Tap,[4] Hans Gelderblom,[3] Silvia Stacchiotti,[5] Jon Greenberg,[6] Dale Shuster,[6] Andrew J. Wagner[7]

[1]Quantitative Clinical Pharmacology and Translational Sciences, Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [2]Metrum Research Group, Tariffville, CT, USA; [3]Leiden University Medical Center, Leiden, Netherlands; [4]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [5]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [6]Global Oncology R&D, Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [7]Dana-Farber Cancer Institute, Boston, MA, USA

INTRODUCTION

Background

- Pexidartinib is a novel oral small-molecule inhibitor that selectively targets colony-stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication mutation[1,2]
- Pexidartinib has demonstrated significant tumor response and improvements in function in patients with symptomatic tenosynovial giant cell tumor (TGCT) that is associated with severe morbidity or functional limitations not amenable to improvement with surgery[3]

Objective

- To develop a population pharmacokinetics (PK) model for pexidartinib in healthy subjects and patients with TGCT
- To identify and estimate effects of potential covariates, such as demographic and clinical factors, that affect pexidartinib PK

METHODS

Data Source and Study Design

- Data were from nine clinical studies with a total of 375 subjects who contributed a total of 8430 PK samples (**Table 1**)
  - Seven phase 1 clinical pharmacology studies in healthy subjects (N = 159), with serial PK samples collected up to 144 hours or 192 hours post-dose
  - Phase 1 Study PLX108-01 in patients with TGCT and other solid tumors (N = 132), with 5 to 6 PK samples per patients collected on Cycle 1 Day 1 and Cycle 1 Day 15, and pre-dose PK samples on Days 1, 8, and 16 of Cycle 1
  - Phase 3 Study PLX108-10 (ENLIVEN) in patients with TGCT (N = 84), with 7 PK samples collected on Cycle 1 Day 15, and random samples on Cycle 3 Day 1 and Cycle 5 Day 1
- Serum concentrations of pexidartinib were determined by a validated liquid chromatography-tandem mass spectrometry method, with lower limit of quantification (LLOQ) of 2.5 ng/mL

Table 1. Summary of Studies Included in Population PK Analysis

Study	Phase	N	Number of PK Samples	Description	Dose Regimen
U114	1	30	1728	Relative BA study in HV	400 mg single doses
U116	1	36	1824	Relative BA study in HV	600 mg single doses
U117	1	18	1119	Dose proportionality study in HV	200, 400, and 600 mg single doses
U118	1	16	334	Drug-drug interaction with itraconazole in HV	600 mg single doses
U119	1	16	333	Drug-drug interaction with rifampin in HV	600 mg single doses
U120	1	16	323	Drug-drug interaction with esomeprazole in HV	600 mg single doses
U121	1	27	589	Food effect study in HV	1200, 1800, 2400 mg
PLX108-01	1	132	1726	Dose-ranging study in patients with TGCT or other solid tumor	200 to 1200 mg/day
ENLIVEN	3	84	454	Phase 3 study in patients with TGCT	Part 1: 1000 mg/day for 2 weeks, followed by 800 mg/day Part 2: 800 mg/day

Phase 1 formulation was used in studies PLX108-01 and U114, whereas phase 3 formulation was used in all other studies.
BA = bioavailability, HV = healthy volunteers, N = number of subjects, PK = pharmacokinetics, TGCT = tenosynovial giant cell tumor.

Population PK Analysis

- The structural PK model was a two-compartment model with sequential zero- and first-order absorption and lag time, and linear elimination from the central compartment
- Inter-individual variability (IIV) was included on clearance from central compartment (CL/F), central volume of distribution (V2/F), peripheral volume of distribution (V3/F), inter-compartmental clearance (Q/F), and absorption rate constant (Ka)
- Inter-occasion variability (IOC) was added to Ka and relative bioavailability (F1)
- A proportional residual error model was used to describe the residual variability
- The following covariates were evaluated on the absorption and/or disposition parameters using a full-model approach:
  - Subject demographics (age, sex, body weight, and race)
  - Liver and renal function parameters (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBIL], serum creatinine clearance [CRCL])
  - Drug formulations (phase 1 vs. phase 3 formulation)
  - Study populations (healthy volunteers vs. patients)
- The final full model was assessed by goodness-of-fit plot and visual predictive check

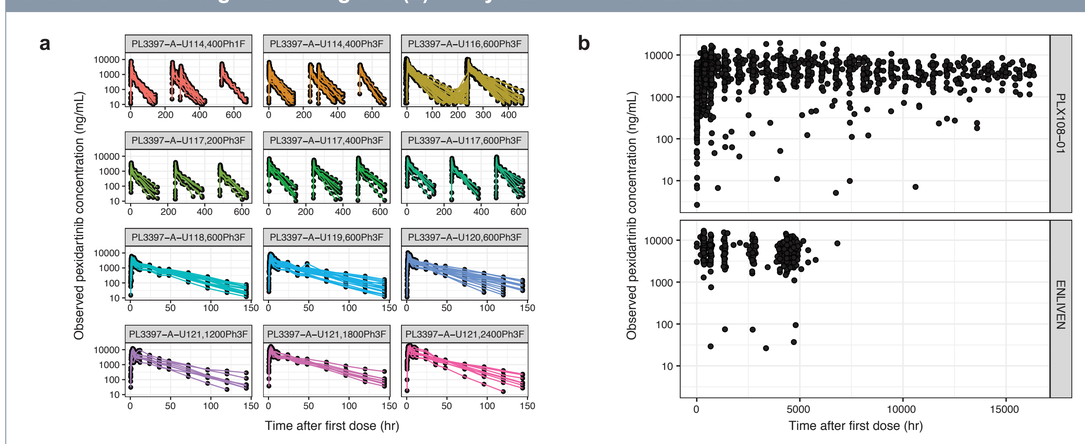
PK Simulations

- Based on the final population PK model and individual post hoc PK parameters, the area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) were generated for the dose regimen of 800 mg/day (400 mg BID) in the ENLIVEN Study

RESULTS

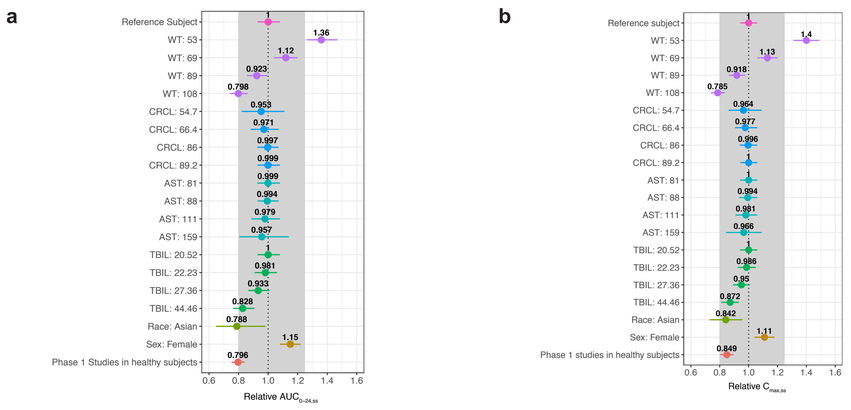
- Observed concentration-time profiles of pexidartinib showed:
  - A bi-exponential decay of pexidartinib concentrations, viewed on a semi-log scale plot (**Figure 1a**)
  - Steady-state concentrations of pexidartinib were maintained over time upon multiple dosing (**Figure 1b**)

Figure 1. Observed Concentration-Time Profiles of Pexidartinib in (a) Healthy Subjects Following Single Oral Dose of 200 mg to 2400 mg and (b) Study PLX108-01 and ENLIVEN Patients



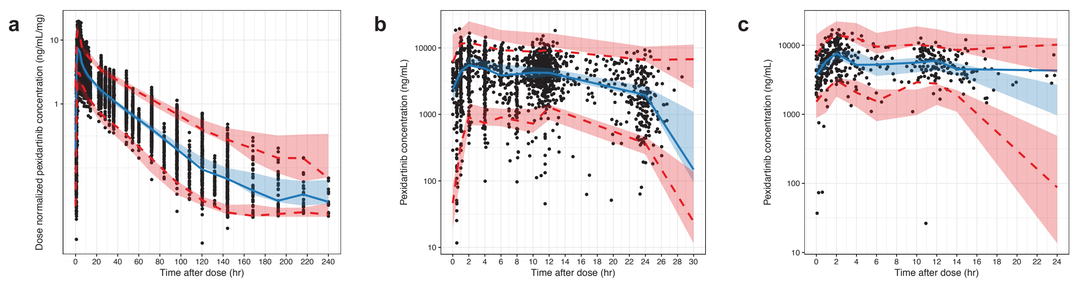
- Covariate effects on pexidartinib exposure are illustrated by the forest plots (**Figure 2**):
  - Model estimated a 21% lower steady-state AUC from 0-24 hours ($AUC_{0\text{-}24,ss}$) of pexidartinib in healthy subjects compared with patients
  - Effect of race (Asian vs. non-Asian) on $AUC_{0\text{-}24,ss}$ fell partially outside the range of 80% to 125%, but with a wide 95% confidence interval
  - All other covariates (sex, CRCL, AST, TBIL) showed a less than 20% effect on pexidartinib exposure, except WT, for which a low value of 53 kg resulted in an approximately 36% increase in $AUC_{0\text{-}24,ss}$ compared with the median value of 80 kg
  - Current analysis dataset included a relatively narrow range of CRCL values and a small number of renally impaired subjects, which have limited the evaluation of CRCL effect
  - Covariate effects on steady-state C_{max} ($C_{max,ss}$) are similar to those on $AUC_{0\text{-}24,ss}$
- Visual predictive check suggested that the final model described the observed data and was suitable for simulation (**Figure 3**)

Figure 2. Forest Plot of Covariate Effects on Pexidartinib (a) $AUC_{0\text{-}24,ss}$ and (b) $C_{max,ss}$



$AUC_{0\text{-}24,ss}$ and $C_{max,ss}$ were derived for the dose of 800 mg/day. The reference is a male, non-Asian patient with median covariate values of WT 80 kg, CRCL ≥90 mL/min, AST ≤80 U/L, and TBIL ≤20.5 µmol/L. The values shown next to WT, CRCL, AST, and TBIL were the 5th, 25th, 75th, and 95th percentiles of observed values of each covariate. Dots and solid horizontal lines are median and 95% CI of (a) relative $AUC_{0\text{-}24,ss}$ and (b) relative $C_{max,ss}$. The gray-shaded region represents 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 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).

Figure 3. Visual Predictive Check Plots for (a) Studies in Healthy Subjects, (b) Study PLX108-01, and (c) ENLIVEN Study



The observed pexidartinib concentrations (ng/mL) are plotted (black dots) versus time after dose (hr) with the 5th (red dashed line), 50th (blue line), and 95th (red dashed line) percentiles of the observed data. Blue-shaded area represents the 95% prediction band of the simulated median, and red-shaded areas represent the 95% prediction bands of the simulated 5th and 95th percentiles.

- Final full model included the following covariate-parameter relationships (**Table 2**):
  - Body weight (WT); sex; race (Asian [N = 8] vs. non-Asian [N = 367]); baseline values of CRCL, AST, and TBIL; and study population (healthy subjects vs. patients) on CL/F
  - WT on Q/F, V2/F, and V3/F
  - A formulation effect on F1 was fixed in the model to account for a 17% higher observed pexidartinib exposure with the phase 3 formulation compared with the phase 1 formulation

Table 2. Parameter Estimate From the Final Population PK Model for Pexidartinib

Parameter CL/F(exp(θ1))	Estimate*	95%CI**
$CL/F(\exp(\theta_1))$	5.83 L/hr	(5.43, 6.27)
$\cdot (WT/80)^{0.75}$		
$\cdot (CRCL_{<90}/90)^{\theta 9}$	-0.0941	(-0.402, 0.214)
$\cdot (Asian)\cdot\exp(\theta_{10})$	1.27	(1.05, 1.54)
$\cdot (AST_{>80}/80)^{\theta 11}$	0.0709	(-0.180, 0.322)
$\cdot (TBIL_{>20.5}/20.5)^{\theta 12}$	0.244	(0.183, 0.306)
$\cdot (StHT)\cdot\exp(\theta_{13})$	1.26	(1.16, 1.36)
$\cdot (Female)\cdot\exp(\theta_{14})$	0.869	(0.808, 0.934)
$V_c/F(\exp(\theta_2))$	98.0 L	(90.0, 107)
$\cdot (WT/80)^{1}$		
$V_p/F(\exp(\theta_3))$	116 L	(106, 128)
$\cdot (WT/80)^{1}$		
$Q/F(\exp(\theta_4))$	20.7 L/hr	(17.9, 23.8)
$\cdot (WT/80)^{0.75}$		
$KA(\exp(\theta_5))$	6.82 hr−1	(5.09, 9.14)
$ALAG1(\exp(\theta_6))$	0.387 hr	(0.385, 0.390)
$D1(\exp(\theta_7))$	1.22 hr	(1.20, 1.25)
$F1_{Phase1}(\exp(\theta_8))$	0.855 Fixed	
$\Omega_{1,1}CL/F$	0.0860 (%CV = 30)	(0.0633, 0.109)
$\Omega_{2,1}COV_{V_c/F-CL/F}$	0.0774 (corr = 0.504)	(0.0425, 0.112)
$\Omega_{2,2}V_c/F$	0.274 (%CV = 56.1)	(0.207, 0.341)
$\Omega_{3,1}COV_{V_p/F-CL/F}$	0.0149 (corr = 0.110)	(-0.0178, 0.0476)
$\Omega_{3,2}COV_{V_p/F-V_c/F}$	-0.0467 (corr = -0.193)	(-0.105, 0.0111)
$\Omega_{3,3}V_p/F$	0.213 (%CV = 48.8)	(0.152, 0.275)
$\Omega_{4,4}Q/F$	0.406 (%CV = 70.8)	(0.271, 0.541)
$\Omega_{5,5}KA$	1.31 (%CV = 165)	(0.648, 1.98)
$\Omega_{6,6}Ph1Form$	0.101 (%CV = 32.6)	(0.0592, 0.143)
$\Omega_{7,7}$IOV $KA(\eta_{7-11})$	1.83 (%CV = 229)	(1.26, 2.40)
$\Omega_{12,12}$IOV $F1(\eta_{12-21})$	0.0652 (%CV = 25.9)	(0.0560, 0.0743)
$\Sigma_{1.1,prop,pat}$ (ε1)	0.0883 (%CV = 29.7)	(0.0839, 0.0927)
$\Sigma_{2.2,prop,ht}$ (ε2)	0.0384 (%CV = 19.6)	(0.0377, 0.0391)

*Estimates of θ modeled in the log domain were exponentiated and are reported in the table.
**95% CI was derived from standard errors obtained from the NONMEM $COVARIANCE step.
AST = aspartate aminotransferase (U/L), ALAG1 = lag time, CI = confidence interval, CL/F = apparent clearance, CV = coefficient of variation, corr = correlation, COV = covariance, CRCL = creatinine clearance (mL/min), D1 = duration of zero-order deposition, $F1_{Phase1}$ = relative bioavailability of Phase 1 formulation to Phase 3 formulation, IOV = inter-occasion variability (variance), KA = first-order absorption rate constant, PK = pharmacokinetic, Q/F = apparent inter-compartmental clearance, StHT = Phase 1 studies with healthy subjects, TBIL = total bilirubin (µmol/L), Vc/F = apparent central compartment volume, Vp/F = apparent peripheral compartment volume, WT = body weight (kg), θ = fixed effect parameter, Ω = inter-individual covariance matrix, $\Omega_{6,6}$Ph1Form = inter-individual variability of F1 for the Phase 1 formulation, $\Sigma_{1.1,prop,pat}$ = proportional residual variability for studies in patients, $\Sigma_{1.1,prop,ht}$ = proportional residual variability for Phase 1 studies in healthy subjects.

- For the dose regimen of 800 mg/day (400 mg BID) in the ENLIVEN Study, the mean of individual pexidartinib $AUC_{0\text{-}12}$ was 77465.1 hr*ng/mL at steady state and 21529.3 hr*ng/mL on Day 1, representing an accumulation ratio of 3.5 (**Table 3**)

Table 3. Post Hoc PK Parameters of Pexidartinib in the ENLIVEN Study

Treatment	PK variables	Mean (SD)	Median (P5-P95)
800 mg/day	$AUC_{0\text{-}12h}$ (hr*ng/mL) on Day 1	21529.3 (5231.1)	20737.7 (14011.5-30731.2)
800 mg/day	$AUC_{0\text{-}12h}$ (hr*ng/mL) at steady state	77465.1 (24974.6)	72462.7 (47845.9-127464.3)
800 mg/day	C_{max} (ng/mL) on Day 1	3523.6 (1093.1)	3247.8 (2188.4-5384.6)
800 mg/day	C_{max} (ng/mL) at steady state	8625.3 (2745.7)	7992.8 (5373.6-13834.1)
800 mg/day	Accumulation ratio	3.6 (0.8)	3.5 (2.7-4.5)
800 mg/day	CL/F (L/hr)	5.6 (1.6)	5.5 (3.1-8.4)

$AUC_{0\text{-}12h}$ = area under the plasma concentration-time curve from zero to 12 hours, C_{max} = maximum plasma concentration, CL/F = apparent clearance, SD = standard deviation, PK = pharmacokinetic, P5 = 5th percentile, P95 = 95th percentile.

CONCLUSIONS

- A population PK model was successfully developed for pexidartinib. No clinically meaningful effects on pexidartinib exposure were identified for demographic characteristics, such as WT, sex, race, study population (healthy subjects vs. patients), and renal and hepatic functional parameters
- Evaluation of renal function effect was limited by the analysis dataset, which included a relatively narrow range of CRCL values and a limited number of renally impaired subjects. Therefore, results from a dedicated renal impairment study should be considered in conjunction with current analysis for dose recommendations in renal impairment subjects
- The model was also used to generate individual exposure metrics in subsequent exposure-response analyses

REFERENCES

1. Turalio (pexidartinib capsules) [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo, Inc; 2019.
2. Tap WD, Wainberg Z, Anthony SP, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N Engl J Med*. 2015;373:428-437.
3. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial cell tumour (ENLIVEN): a randomized phase 3 trial. *Lancet*. 2019;394(10197): 478-487.

Sponsored by Daiichi Sankyo, Inc.
Poster presented at the Tenth American Conference on Pharmacometrics (ACoP10), Orlando, Florida.
The authors wish to thank SciStrategy Communications for assistance in the development of this poster.

For questions or information regarding this poster, please contact Dr Ophelia Yin at oyin@dsi.com.