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Population Pharmacokinetic Analysis for Comparison of Pexidartinib Exposure in Asian and Non-Asian Patients

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INTRODUCTION

Background and Objectives

- 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]
- A pooled population pharmacokinetic (PK) analysis of pexidartinib in healthy subjects and patients with TGCT or other solid tumors was previously described[4]
- This report presents an updated analysis, including three additional studies with Asian patients, to further evaluate the population PK and the exposure of pexidartinib and its glucuronide metabolite (ZAAD-1006a) in Asian and non-Asian patients

METHODS

Data Source and Study Design

- Data were from 12 clinical studies with a total of 422 subjects who contributed a total of 9202 pexidartinib PK samples and 3828 ZAAD-1006a PK samples **(Table 1)**
  - In healthy subjects, pexidartinib was given as a single oral dose of 200 mg to 2400 mg, and in patients it was given as multiple oral doses of 200 mg/day to 1200 mg/day
  - 30 of 422 subjects (7.11%) were Asian, of whom 3 were healthy subjects enrolled in phase 1 clinical studies and 27 were patients **(Table 2)**
- Subject demographic and baseline characteristics are summarized in **Table 3**
- Plasma concentrations of pexidartinib and ZAAD-1006a were determined by the validated liquid chromatography–tandem mass spectrometry methods
  - The lower limit of quantification (LLOQ) of pexidartinib was 2.5 ng/mL in study PLX108-01, and 10 ng/mL in all other studies
  - The LLOQ of ZAAD-1006a was 10 ng/mL in all studies

Table 1. Summary of Studies Included in the Updated Population PK Analysis

Study	Phase	N	Number of PK Samples for Pexidartinib	Number of PK Samples for ZAAD-1006a	Description	Dose Regimen
Studies included in the previous pooled population PK analysis[4]						
U114*	1	30	1728	NA	Relative BA study in HV	400 mg single doses
U116	1	36	1824	NA	Relative BA study in HV	600 mg single doses
U117	1	18	1119	1122	Dose proportionality study in HV	200, 400, and 600 mg single doses
U118	1	16	334	333	Drug-drug interaction with itraconazole in HV	600 mg single doses
U119	1	16	333	331	Drug-drug interaction with rifampin in HV	600 mg single doses
U120	1	16	323	320	Drug-drug interaction with esomeprazole in HV	600 mg single doses
U121	1	27	589	587	Food effect study in HV	1200, 1800, 2400 mg
PLX108-01*	1	132	1726	NA	Dose-ranging study in patients with TGCT or other solid tumor	200 to 1200 mg/day
ENLIVEN	3	84	454	453	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
Additional studies included in this updated analysis						
A103	1	11	148	142	Phase I study in Asian patients with advanced solid tumors	Cohort 1: 600 mg/day Cohort 2: 1000 mg/day for 2 weeks, followed by 800 mg/day
U126	1	30	559	540	Drug-drug interaction with midazolam and tolbutamide in patients with TGCT	800 mg/day
PLX108-13	1	6	65	NA	Phase 1/2 study in patients with melanoma	1000 mg/day or 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 subjects, N = number of subjects, NA = not available, PK = pharmacokinetics, TGCT = tenosynovial giant cell tumor.

Table 2. Summary of Studies by Population and Race

Study	Population		Race	
	Healthy Subjects	Patients	Asian	Non-Asian
U114	30	0	1	29
U116	36	0	2	34
U117	18	0	0	18
U118	16	0	0	16
U119	16	0	0	16
U120	16	0	0	16
U121	27	0	0	27
PLX108-01	0	132	5	127
ENLIVEN	0	84	0	84
A103	0	11	11	0
U126	0	30	5	25
PLX108-13	0	6	6	0

Table 3. Summary of Subject Demographic and Baseline Characteristics

Characteristic	Healthy Subjects (n = 263)	Patients (n = 159)	Total (N = 422)
Age, median (range) years	38 (18, 60)	52 (18, 84)	45 (18, 84)
Sex, n (%)			
Male	130 (82)	124 (47)	254 (60)
Female	29 (18)	139 (53)	168 (40)
Race, n (%)			
White	72 (45)	220 (84)	292 (69)
Black or African American	77 (48)	7 (3)	84 (20)
Asian	3 (2)	27 (10)	30 (7)
American Indian or Alaska Native	1 (1)	3 (1)	4 (1)
Native Hawaiian or other Pacific Islander	1 (1)	2 (1)	3 (1)
Other	5 (3)	4 (1)	9 (2)
Weight, median (range), kg	79.3 (50.9, 106.8)	77.2 (31.8, 165.3)	78.6 (31.8, 165)
Liver function variables, median (range)			
ALT, U/L	17.0 (9.0, 38.0)	17.0 (4.0, 101.0)	17.0 (4.0, 101.0)
AST, U/L	19.0 (12.0, 40.0)	19.0 (9.0, 188.0)	19.0 (9.0, 188.0)
TBIL, mg/dL	8.6 (1.7, 20.5)	6.8 (1.7, 31.0)	7.0 (1.7, 31)
CRCL, median (range), mL/min	114.0 (76.4, 150.0)	111.0 (33.9, 150.0)	113 (33.9, 150.0)
Formulation, n (%)			
Phase 3 formulation	144 (91)	131 (50)	275 (65)
Phase 1 formulation	15 (9)	132 (50)	147 (35)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CRCL = creatinine clearance, TBIL = total bilirubin.

METHODS (CONT)

Population PK Analysis

- Pexidartinib structural model
  - 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 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 was added to Ka and relative bioavailability (F1)
  - A proportional residual error model was used to describe the residual variability
- ZAAD-1006a structural model
  - Plasma concentration data of ZAAD-1006a was modeled separately, using the same structural model as that for pexidartinib
  - The fraction of ZAAD-1006a formation was treated as F1 in the model, which represented the fraction of pexidartinib dose to form the metabolite ZAAD-1006a. It was fixed to 0.38 based on results from the mass balance study PL3397-A-U115
- The following covariate effects were estimated for pexidartinib and ZAAD-1006a using a full model approach:
  - Body weight; sex; race (Asian vs. non-Asian); baseline values of creatinine clearance, aspartate aminotransferase, and total bilirubin; and study population (healthy subjects vs. patients) on CL/F
  - Body weight on Q/F, V2/F, and V3/F
  - A formulation effect on F1 was fixed in the pexidartinib model to account for a 17% higher observed pexidartinib exposure with the phase 3 formulation compared with the phase 1 formulation

PK Simulations

- Based on the population PK models and individual post hoc PK parameters, steady state exposures of pexidartinib and ZAAD-1006a in individual subjects were generated for the dose regimen of 800 mg/day (400 mg BID)
- Comparison of pexidartinib and ZAAD-1006a exposure was made between Asian and non-Asian patients, since there were only 3 Asians in the healthy subject population

RESULTS

- Observed concentrations of pexidartinib and ZAAD-1006a in Asian subjects were within the overall concentration range in all subjects **(Figures 1 and 2)**
- Both race (Asian vs. non-Asian) and body weight are covariates on pexidartinib CL/F
  - Asian race alone had 28% higher CL/F
  - On average, Asian patients had approximately 24% lower body weight
    - Median (range): 60.2 (43.0, 84.0) kg in Asian versus 79.6 (31.8, 165) kg in non-Asian patients
  - Therefore, pexidartinib CL/F is estimated to be 5.97 L/hr for a typical Asian patient with body weight of 60 kg, comparable to the estimated value of 5.79 L/hr for a typical non-Asian patient with body weight of 80 kg
- When comparing Asian versus non-Asian patients, model-predicted steady state area under the concentration-time curve over 24 hours ($AUC_{0\text{-}24h}$) of pexidartinib and ZAAD-1006a were found to be similar between the two groups **(Figure 3, Table 4)**

Figure 1. Observed Concentration-Time Profiles of Pexidartinib and ZAAD-1006a from All Studies Including Healthy Subjects and Patients: Time After (a) First Dose and (b) Dose on Day 1 and Post-Day 1

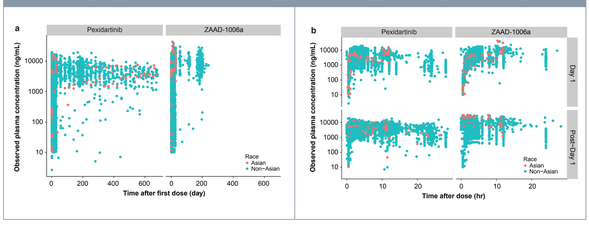


Figure 2. Observed Concentration-Time Profiles of Pexidartinib and ZAAD-1006a from Patient Studies: Time After (a) First Dose and (b) Dose on Day 1 and Post-Day 1

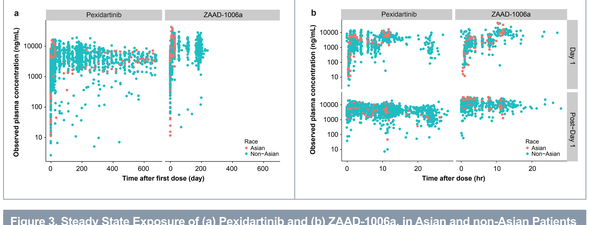
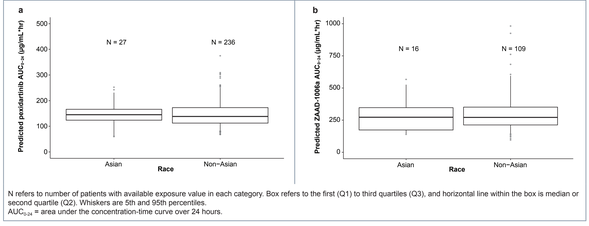


Figure 3. Steady State Exposure of (a) Pexidartinib and (b) ZAAD-1006a, in Asian and non-Asian Patients



N refers to number of patients with available exposure value in each category. Box refers to the first (Q1) to third quartiles (Q3), and horizontal line within the box is median or second quartile (Q2). Whiskers are 5th and 95th percentiles.
$AUC_{0\text{-}24}$ = area under the concentration-time curve over 24 hours.

Table 4. Comparison of Pexidartinib and ZAAD-1006a $AUC_{0\text{-}24h}$ (μg*hr/mL) Between Asian and Non-Asian Patients

	Pexidartinib			ZAAD-1006a		
Race	N	Mean	Median (P5-P95)	N	Mean	Median (P5-P95)
Asian	27	147	145 (63.4-231)	16	292	273 (145-526)
Non-Asian	236	149	138 (82.3-250)	109	354	271 (144-595)

$AUC_{0\text{-}24h}$ = area under the plasma concentration-time curve from zero to 24 hours, P5 = 5th percentile, P95 = 95th percentile.

CONCLUSIONS

- Analysis suggests that exposures for pexidartinib and its glucuronide metabolite (ZAAD-1006a) are similar between Asian and non-Asian patients

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