Population Pharmacokinetics of PF-04447943 in Healthy Volunteers and Adult Patients with Alzheimer's Disease or Sickle Cell Disease

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Objectives

PF-04447943 is a selective inhibitor of the cyclic guanosine monophosphate (cGMP)-specific PDE9A enzyme, being developed for the prophylactic treatment of Sickle Cell Disease (SCD). The purposes of our analyses were to characterize PF-04447943 pharmacokinetics (PK) in healthy volunteers (HV) and adult patients with Alzheimer's disease (AD) or SCD and to identify factors that may differentiate the populations treated and impact the PK relationship of PF-04447943.

Methods

A total of 10 studies (7 in HV, 2 in AD and 1 in SCD patients) were included in the analyses. Subjects received single or multiple doses (BID) of PF-04447943 ranging from 1 mg to 150 mg. Plasma concentrations over time were analyzed using a nonlinear mixed effects modeling approach (NONMEM). The first order conditional estimation with interaction (FOCEI) method was used throughout. Potential covariates (body weight (BWT), age, gender, disease state, race, food, formulation and creatinine clearance) were evaluated using stepwise inclusion/deletion as implemented in the Stepwise Covariate Model (SCM)[1] building procedure in PsN. Prediction-corrected visual predictive checks were used to assess model performance.

Simulations were performed utilizing the final PK model to explore covariates effects on the exposure parameters, C_{max} (maximum concentration) and area under the curve ($AUC_{0-\infty}$).

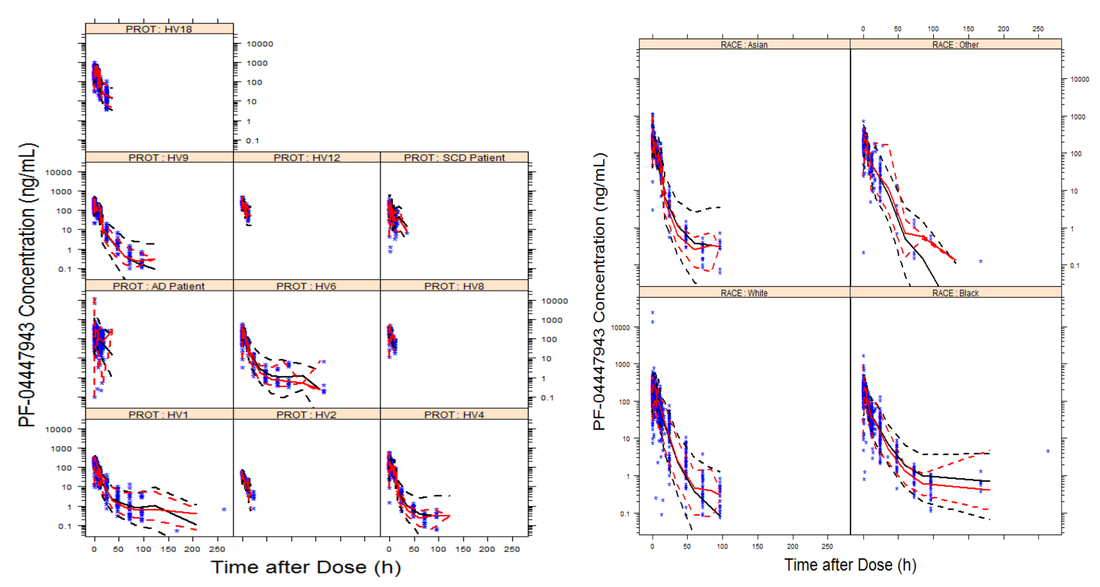
Results

A total of 261 subjects (163 male and 98 female); including 142 White, 64 Black, 31 Asian and 24 other race, with 3467 concentration records were analyzed. The PK of PF-04447943 was best characterized by a two-compartment model with 1st order absorption (Ka) with lag time (tlag) and 1st order elimination across the populations from 10 studies (Figure 1). Interindividual variability (IIV) with covariance terms were included for clearance (CL/F), central (V_1/F) and peripheral (V_2/F) volume and distributional clearance (Q/F), and Ka. Residual random effect was described with a proportional error model with IIV. BWT was incorporated as a structural covariate on CL/F, V_1/F, V_2/F and Q/F. The other covariates identified were age on CL/F; race on V_2/F; race, sex and population on Q/F and age and food on Ka. PK parameters were well estimated with relative small relative standard error (RSE) (Table 1). The parameter estimates for a typical healthy white male (70 kg and 40 years) under fasted conditions were 13.9 L/h, 87.3 L, 7.61 L, 0.546 L/h, 4.7 h^{-1} and 0.196 h for CL/F, V_1/F, V_2/F, Q/F, Ka and tlag, respectively. Feeding reduced Ka by 89.9%. Black subjects showed a 11-fold higher V_2/F and a 3.5 fold higher Q/F than White subjects. In general, prediction corrected VPC plots indicate that the final model predict the data well (Figure 2).

The Black race effect on the exposure was explored and simulations results showed that predicted C_{max} and $AUC_{0-\infty}$ were similar among White, Black and Asian races. Females had similar exposures as males. Exposure parameters were not impacted by disease status and age.

Figure 1. Basic Goodness Fit for the Final Model Stratified by Studies

Figure 2. Prediction Corrected Visual Predictive Check Stratified by Study (left panel) and Race (right panel)



Red and black solid and dashed lines represent the median and the 2.5th and 97.5th percentiles of the observed and simulated data, respectively. Blue dots are observed data.

Table 1. Key Parameter Estimates for the Final Model

Parameter	Estimate	RSE %	IIV %	RSE %
Ka (h^{-1})	4.7	10.21	98.13	10.18
CL/F (L/h)	13.9	2.14	28.98	6.51
V1/F (L)	87.3	1.25	13.34	9.1
V2/F (L)	7.61	8.16	60	9.82
Q/F (L/h)	0.546	10.88	49.09	10.75
Lag time (h)	0.196	4.76		
Age_Ka	0.742	26.68		
Food_fed_Ka	-0.899	2.61		
Food_WRF_Ka	-0.833	3.05		
Age_CL/F	-0.155	24.26		
Black Race_V2/F	10.2	14.8		
Asian Race_V2/F	2.51	15.26		
Black Race_Q/F	2.54	18.78		
Asian Race_Q/F	0.942	32.38		
Female_Q/F	-0.316	19.34		
Patient_Q/F	1.5	15.73		
Proportional error (%)				
HV studies	15	4.43	51.67	7.85
AD patient study	43.6	13.9	84.68	8.79
SCD patient study	24.8	21.25		

Continuous covariates (eg age) were included in the model as a power function: $\theta_i = \theta_{pop} * (COV_i/COV_{median})^{**} \theta_{x,cov}$
Categorical covariates (eg Black, Asian, Female, Food, Patient) were introduced in the model as $\theta_i = \theta_{pop} * (1 + \theta_{x,cov})$ if $cov_i = X_l$
Note: WRF: without regard to food

Conclusions

The proposed population PK model adequately describes the available data on PF-04447943. Although a few statistically significant covariates were identified they are not expected to result in clinically relevant differences in exposure. Understanding of the PK of PF-04447943 across a range of populations will assist future drug development.

References

[1] Jonsson EN, Karlsson MO. Automated covariate model building within NONMEM. Pharm Res (1988) **15**: 1463–1468.

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