Title: POPULATION PHARMACOKINETIC MODELING OF FOSAMPRENAVIR IN PEDIATRIC HIV- INFECTED PATIENTS

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Objectives: The primary purpose of this analysis was to characterize the pharmacokinetics (PK) of fosamprenavir (FPV) with or without ritonavir (RTV) in pediatric patients infected with the Human Immunodeficiency Virus (HIV) and describe factors which may influence amprenavir (APV) PK in order to simulate FPV and FPV/RTV dosing regimens that deliver target plasma APV exposures in this population.

Methods: A population PK database was developed from three Phase II, open-label, multiple-dose (MD), studies conducted in HIV-1 infected pediatric patients. FPV was administered to protease inhibitor (PI) naïve and PI-experienced pediatric subjects with or without concomitant administration of RTV. Patients who received FPV BID could be 2 to <6 years of age while those who received FPV+RTV BID or QD could be 4 weeks to 18 years of age. FPV and RTV were administered as an oral suspension and solution, respectively, with food or as a tablet (FPV) or capsule (RTV) formulation with or without food. Plasma APV concentration data collected in each study included a single extensive PK sampling day for most patients following at least 10 days of MD therapy and up to 9 subsequent study visits where a single trough sample was collected. Observed values of any time dependent covariates were inserted chronologically in the population PK dataset with linear interpolation for data records in between observed time points.

Data were analyzed using nonlinear mixed-effects modeling with the NONMEM® software, Version V, Level 1.1 (ICON Development Solutions, Ellicott City, MD). The first-order conditional estimation with INTERACTION option (FOCEI) method in NONMEM® was employed for all model runs. Final model parameter estimates were reported with a measure of estimation uncertainty. A covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented. The performance of the final model was assessed by the predictive check procedure. The model was used to simulate FPV and FPV/RTV dosing regimens that deliver target plasma APV exposures in pediatric patients. Steady-state concentration-time profiles were simulated in 10,000 patients.

Results: The pediatric FPV population dataset was comprised of 137 patients contributing 1322 plasma APV concentrations. The study population consisted of 62 males and 75 females with baseline ages ranging from 8 months to 18 years and baseline weights ranging from 5.9kg to 102.8kg. The majority of patients were Caucasian, though races such as Black, Asian, Hispanic, American Indian and other races were also represented. Baseline α_1-acid glycoprotein (AAG) concentrations ranged from 0.41 to 2.69 g/L. The majority of patients (119) received FPV with RTV while 18 patients received FPV alone.

A two-compartment model with first-order absorption and elimination was chosen as the structural model. Relative bioavailability was estimated separately for the suspension formulation under fasted conditions ($F_{food,sus}$) and for the tablet formulation (F_{tab}) using the suspension formulation under fed conditions as the reference (F). Inter-individual random effect distributions were modeled using multivariate log-normal distribution, with a covariance term between oral clearance (CL/F) and the central compartment volume of distribution (V2/F) and an inter-occasion variance (IOV) term on CL/F. Residual error was described by a combined additive and proportional model.

The typical estimates, precision, and 95% CI of the full PK model parameters for the reference covariate effects (Age>4yr, weight=70Kg, AAG=0.77g/L, Caucasian, Male, Suspension formulation administered with food) are provided in the table below.

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Parameter	Population Estimate	% Standard Error	95%CI	Parameter	Population Estimate	% Standard Error	95%CI
CL/F (FPV/RTV)	34.1 L/hr	7%	(28.9-39.7)	η_{CL} variance	0.0901 (30% CV)	17%	(0.0391-0.145)
CL/F (FPV)	84.4 L/hr	11%	(59.1-109)	$\eta_{CL} - \eta_{V2}$ correlation	0.0945	40%	(-0.0374-0.218)
V2/F	288 L	23%	(160-421)	η_{V2} variance	0.438 (66% CV)	27%	(0.0276-0.968)
Q/F	63.5 L/hr	15%	(41.3-91.2)	$\eta_{IOV,CL}$ variance	0.114 (34% CV)		(0.0679-0.153)
V3/F	1630 L	28%	(882-3110)	η_{Q} variance	0.536 (73% CV)	36%	(0.222-1.02)
Ka	1.13 hr-1	30%	(0.759-1.74)	Proportional Error	0.0827	7%	(0.0528-0.125)
F_{tab}	1.09	8%	(0.906-1.28)	Add error	0.0760	12%	(0.035-0.119)
$F_{food,sus}$	0.870	8%	(0.699-1.1)				

Co-administration with RTV was estimated to decrease FPV CL/F almost 60% (95% CI: 33%-73%). The allometric relationship between weight and FPV/RTV CL/F resulted in a range of population CL/F estimated from 6.6-46.2 L/hr across the weight range in the dataset. Weight-adjusted CL/F was expected to be 1.4-fold greater (upper 95%CI: 2.5-fold) in the youngest children (median age over study duration =1.09 years) as compared to children greater than 4 years of age (precision in the age effect parameters was 26% and 65%). This age effect was similar to that observed with RTV and may represent developmental differences between patients. Typical population FPV/RTV CL/F estimates were expected to range from 22.5 to 51.4- L/hr (9% RSE, 95% CI: 20.2-57.1 L/hr) across the AAG range of 0.4-1.5 g/L. Typical population V2/F estimates were expected to range from 32.1-432 L across the weight range in the dataset and from 189-367 (92% RSE, 95% CI: 164-501) L across the AAG range of 0.4-1.5 g/L.

The typical population estimate of FPV/RTV CL/F (34.1 L/hr) in this pediatric dataset was greater than previously reported in adults (21.5 L/hr). The FPV CL/F estimate of 84.4 L/hr was similar to the previously estimated adult value of 91.8 L/hr. The relationships between AAG and the parameters CL/F and V2/F in this pediatric population were consistent with effects observed in the adult patient population. Model goodness-of-fit criteria indicated that the model adequately described the pediatric data.

The full model was used to simulate plasma APV exposure in pediatric HIV patients. APV exposure was simulated using separate mg/kg FPV doses for various pediatric groups and dosing regimens with maximum FPV doses of 700mg and 1400mg for the FPV/RTV BID regimen and the FPV/RTV QD or FPV BID regimens, respectively. Dosing regimens which minimized variability in exposure and allowed plasma APV exposure in pediatric patients to consistently match historical adult (i.e. target) exposure are presented.

Conclusions: The population PK of orally administered FPV was described by a two-compartment model with first-order absorption and elimination.

The main predictors of plasma APV exposure were the co-administration with RTV, age, body weight, and AAG. The main predictors FPV V2/F were body weight and AAG. The effects of AAG on FPV CL/F and V2/F in pediatric patients were consistent with those in adult patients.

The population PK model and simulations were used to support the approval of FPV and FPV/RTV dosing recommendations for HIV-1 infected children at various age ranges and to support the on-going evaluation of FPV/RTV dosing in children 4 weeks to 6 years of age.

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