Journal of the International AIDS Society

Poster presentation

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Population pharmacokinetic/pharmacodynamic analysis of lopinavir and ritonavir in subjects receiving the tablet formulation

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from Ninth International Congress on Drug Therapy in HIV Infection
Glasgow, UK. 9–13 November 2008

Published: 10 November 2008

Journal of the International AIDS Society 2008, **11**(Suppl 1):P245 doi:10.1186/1758-2652-11-S1-P245

This abstract is available from: http://www.jiasociety.org/content/11/S1/P245

Purpose of the study

Study M05-730 was conducted to compare the safety, tolerability, pharmacokinetics (PK) and antiviral activity for once-daily (QD) and twice-daily (BID) lopinavir/ritonavir (LPV/r) tablet in antiretroviral-naïve subjects. The LPV/r QD regimen was shown to be non-inferior to the BID regimen. This analysis explores the population PK and pharmacodynamics (PD) of the LPV/r tablets in HIV-infected subjects.

Methods

A total of 633 subjects (322 QD and 311 BID) were included in this analysis. Intensive PK samples were obtained in 69 subjects. Sparse PK was obtained up to 48 weeks (up to five samples) in all subjects. The model-predicted ritonavir (RTV) PK parameters [apparent clearance (CL/F), volume of distribution (Vc/F) and absorption rate constant (ka)] were included in the population PK modeling for lopinavir (LPV). Covariate analysis (age, sex, race, weight, body surface area, creatinine clearance, dosing regimen [QD versus BID], hepatitis B/C virus, and alcohol use) was performed for RTV and LPV to identify potential covariates that may alter the PK profile. Individual LPV exposure (maximum concentrations [Cmax], area under the curve [AUC] and predose trough concentrations [Cmin]) was estimated. The relationship between these LPV PK parameters and antiviral efficacy (HIV-1 RNA <50 copies/mL) at week 48 was evaluated using logistic regression.

Summary of results

Table 1 presents the PK results.

None of the tested covariates had an effect on ritonavir PK. The only covariate that had an effect on LPV PK was weight for which a 10-kg increase in weight is estimated to result in a 4% increase in LPV CL/F. There was no association between LPV Cmax, AUC or Cmin vs. virologic efficacy at week 48 ($p > 0.1$).

Conclusion

In summary, only weight had a small, statistically significant but not clinically relevant, effect on LPV CL/F. A priori adjustment in LPV/r dose based on subject characteristics (race, sex, weight, renal function, etc.) is not warranted. The virologic response did not correlate with LPV levels indicating that, even at the lowest levels measured in this trial, the virologic response was maintained.

Table 1:

	Population Estimate (standard error)	
Parameter	**Ritonavir**	**Lopinavir**
CL/F (L/h)	22.79 (0.783)	5.63 (0.11)
Vc/F (L)	244 (20.4)	144 (10.5)
ka (h-1)	0.488	1.22