Pharmacokinetic/Pharmacodynamic Effects of PA-457 In HIV-infected Patients Following A Single Oral Dose

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INTRODUCTION

PA-457 is the first antiretroviral drug candidate in a novel class of 'Maturation Inhibitors'. PA-457 inhibits late stage GAG processing, preventing the emergence of mature viral particles.

OBJECTIVE

To evaluate the PK/PD of single oral doses of PA-457 in HIV-1 infected patients not receiving active antiretroviral therapy.

METHODS

Randomized, double-blind, placebo-controlled, parallel group, single dose study in HIV-1 infected subjects not currently on therapy. 24 adult males received 75, 150, 250 mg PA-457 or placebo orally. Blood samples for pharmacokinetics and viral load determination were collected frequently over 21 days. Plasma was analyzed for PA-457 concentrations by a validated, sensitive LC/MS/MS method; HIV RNA was quantified by the Roche Amplicor assay (LOQ 50 copies/mL).

Candidate pharmacokinetic/pharmacodynamic models were fit to the data using maximum likelihood followed by MAP Bayesian estimation (ADAPT II); model discrimination was by Akaike's Information Criteria, and the data was weighed by the inverse of the estimated error variance.

The final PK/PD model is shown in Figure 1. The pharmacokinetic model was a two-compartment, oral absorption model with a fitted lag time. The final pharmacodynamic model utilized capacity limited viral replication, with drug effect was modeled as inhibiting the rate of viral replication. Pharmacodynamic endpoints included: the absolute and integrated % inhibition of viral replication, and integrated Log HIVRNA reduction from baseline (AUEC).

RESULTS

The fit of the PK and PD models were both excellent, with an R2 = 0.99 and 0.85, respectively. Example fits are shown in Figure 2. Summary statistics for the PK and PD parameters are provided in Tables 1 and 2. The PK of PA-457 was linear, and none of the structural model parameters differed by dose.

Mean (CV%) pharmacodynamic endpoints by dose: Maximum %Inh; (75mg: 33.2(121), 150mg: 45.0 (85), 250mg: 49.6 (65)); Integrated %Inh; 6506(148), 10,080(125), and 7702(79) copies*hr/mL for the 75, 150, and 250mg doses, respectively. The relationship between effect site concentrations and % inhibition is shown in Figure 3. The Area under the effect curve (AUEC) decreased in a dose-dependent manner, with the 75mg dose demonstrating significantly less activity compared to the higher dose levels. The mean reduction in viral load from baselne is shown in Figure 4.

The mean (CV%) AUCe (Area under the curve of drug at the effect site) to AUCp (Area under the curve of drug in the central compartment) ratio ranged between ~1-2%, which is consistent with the protein binding of PA-457.

Figure 1: Pharmacokinetic/Pharmacodynamic Model

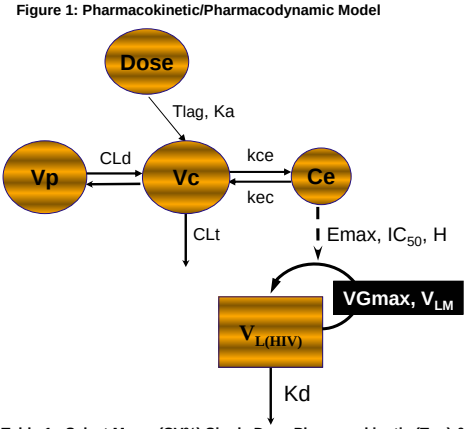


Table 1: Select Mean (CV%) Single Dose Pharmacokinetic (Top) & Pharmacodynamic (Bottom) Parameters for PA-457

Dose	Vss/F (L)	CLt/F (L/h)	TLag (h)	Ka (1/h)	T1/2 (h)
75 mg	13.9 (14)	0.17 (29)	0.18 (49)	3.8 (47)	63.9 (12)
150 mg	12.0 (3.8)	0.16 (8.0)	0.20 (7)	3.4 (49)	55.1 (10)
250 mg	14.0 (19)	0.17 (15)	0.15 (11)	3.7 (30)	62.1 (15)
All data	13.3 (15)	0.17 (18)	0.17 (31)	3.6 (40)	60.3 (14)
	VGmax (copies/h)	VLm (copies/mL)	Ce50 (ng/mL)	Kec ($1/h \cdot 10^3$)	Kce ($1/h \cdot 10^3$)
75 mg	1621 (84)	1093 (14)	52.8 (50)	6.0 (26)	0.15 (73)
150 mg	2059 (54)	1097 (23)	65.8 (18)	5.6 (25)	0.12 (60)
250 mg	2340 (58)	1091 (21)	59.6 (47)	6.2 (11)	0.10 (61)
All data	2007 (62)	1094 (18)	59.4 (38)	6.0 (21)	0.12 (69)

Vss/F, apparent steady-state volume of distribution; CLt/F, oral clearance; T1/2, half-life; TLag, lag time prior to the onset of oral absorption; Ka, rate constant for oral absorption

VGMAX; maximal velocity of viral replication; VLm, median HIVRNA copy number resulting in half-maximal replication; CE50, concentration of PA-457 in the effect site which inhibits 50% of viral replication; Kec & Kce, rate constants for transfer of PA-457 between the effect sites (e) and central (plasma) compartment (c)

Figure 2: Fit of the Pharmacokinetic (top) and Pharmacodynamic (bottom) Model in a Representative Patient.

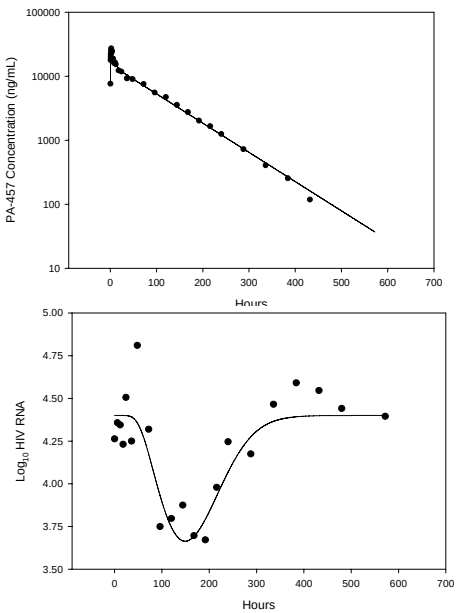


Figure 3: Area Under the HIVRNA Effect Curve (AUEC) vs. Dose

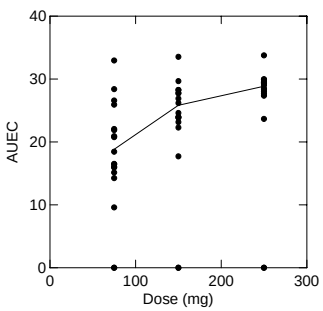
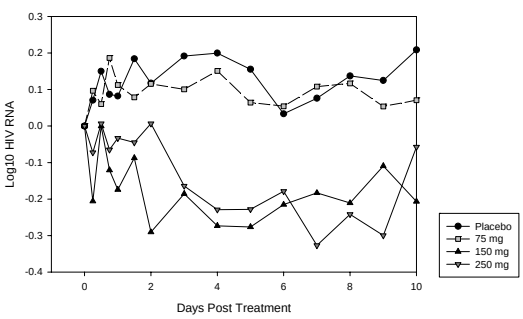


Figure 4: Mean Reduction in Viral Load by Dose



CONCLUSIONS

PA-457 was well tolerated in this group of HIV-infected patients, and demonstrated a dose-related reduction in viral load following a single dose. PA-457 exhibits a very long half-life, suggesting once daily dosing would be reasonable. The pharmacokinetics were well characterized by a 2-compartment, oral absorption model, and these results were similar to previous studies in healthy volunteers.

The pharmacodynamics of PA-457 were well characterized with a model incorporating an effect site, capacity-limited viral replication, with PA-457 inhibiting replication of HIV-1. Compared to plasma concentrations, the antiviral activity of PA-457 was more was closely linked to a hypothesized effect site, which may represent free PA-457 at the site of drug action.

Multiple dose studies of PA-457 in HIV-infected adults are ongoing.