PK-PD Modelling to Support Go/No Go Decisions for a Novel gp120 Inhibitor

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INTRODUCTION

PF-00821385 is a specific inhibitor of HIV-1 gp120 mediated cell-cell fusion. Inhibitors of HIV-1 gp120 represent a novel mechanistic approach with the promise of activity against both CXCR4 and CCR5-using B-clade viruses.

A pharmacokinetic-pharmacodynamic (PK-PD)-disease model has been previously developed to describe the viral load-time profile in HIV infected patients after short term treatment with CCR5 antagonists[1].

This disease model incorporated historical and preclinical data as well as pharmacokinetic data collected from a Phase I study to evaluate, by simulation, the possible range of efficacious doses and regimens of PF-00821385.

OBJECTIVES

- To describe the population pharmacokinetics PF-00821385 in healthy male volunteers following single ascending doses
- To predict a likely oral dose to achieve a 1.5 log drop in viral load following 10 days of treatment using a PK-PD-Disease model

STUDY DESIGN

- Single doses of PF-00821385 were administered as an oral suspension in two cohorts of 12 healthy male subjects. The starting dose was 3mg and doses were escalated to 1300 mg using a placebo controlled escalating design.
- The final period for the 2nd cohort included a non-randomised administration of PF-00821385 (500mg) together with a high fat meal.
- Plasma pharmacokinetic samples were collected at intervals up to 72 hours in 24 healthy Asian male volunteers.

METHODS

Pharmacokinetics (PK)

- Population PK analysis of PF-00821385 from first in human study.
- One and two compartment disposition model, parameterized as clearances and volumes, with first-order absorption and fitted to log-transformed PF-00821385 concentrations.
- Parameter estimation was performed using first-order conditional estimation (FOCE) with interaction with NONMEM V level 1.1.

Pharmacodynamics (PD)

- Inhibitory Emax model was used for the inhibition of viral infectivity rates based on the *in vitro* data of viral growth inhibition.
- Based on the ViroLogic assay data, median EC90 (124nM) and cut-off EC90 (500nM) were chosen to target
  - (a) 90% response in the pool of clinical virus isolates (n=25);
  - (b) Inhibition of viral replication in >70% of patients infected with a Clade B virus.
- *In vivo* IC50 (121 ng/mL and 489 ng/mL) were obtained from observed EC90 and corrected by molecular weight (422 g/mol), plasma protein binding (45% unbound) and *in vitro* basic reproductive ratio (BRR=2 *in vitro* versus approximately 7 in patients).

Disease Model

- A published model[2] described the viral load-time profile in the presence of anti-HIV drugs with various mechanisms of action.
- The simplified disease model described the followings:
  - Conversion of uninfected T cells to actively infected CD4+ cells
  - Conversion of uninfected T cells to latently infected CD4+ cells
  - Conversion of latently infected CD4+ cells to actively infected CD4+ cells
  - Death of uninfected T cells, virus, actively and latently infected CD4 cells

		Dual Cell Line		Single Cell Lines	
Virus	Tropism	IC50 (nM)	IC90 (nM)	IC50 (nM)	IC90 (nM)
04-116871_VL_781.69	R5	2	**12**	2	**9**
04-116884_VL_328.45	R5	2	**13**	2	**9**
04-116877_VL_938.28	R5	4	**18**	4	**21**
04-116873_VL_754.51	R5	4	**22**	4	**21**
04-116868_VL_518.14	R5	5	**21**	5	**26**
04-116870_VL_181.51	R5	8	**38**	8	**44**
04-116889_VL_440.85	Dual	9	**47**	12	**55**
04-116874_VL_560.34	R5	10	**52**	12	**71**
04-116882_VL_624.75	R5	23	**119**	15	**106**
04-116869_VL_833.52	R5	14	**83**	15	**122**
04-116890_VL_781.45	Dual	15	**143**	22	**170**
04-116885_VL_530.54	R5	20	**135**	22	**178**
04-116875_VL_279.69	R5	30	**137**	25	**213**
04-116879_VL_988.03	R5	22	**129**	29	**242**
04-116881_VL_338.52	R5	46	**226**	56	**299**
04-116893_VL_193.95	X4	25	**202**	39	**354**
04-116867_VL_837.51	R5	42	**289**	46	**383**
04-116876_VL_969.72	R5	66	**277**	73	**436**
04-116872_VL_186.32	R5	188	1774	292	>2222
04-116880_VL_696.65	R5	444	2041	595	>2222
04-116886_VL_578.66	Dual	571	>2222	503	>2222
04-116888_VL_113.66	R5	715	>2222	1470	>2222
04-116892_VL_534.93	X4	1041	>2222	1135	>2222
04-116878_VL_241.32	R5	>2222	>2222	>2222	>2222
04-116883_VL_432.63	R5	>2222	>2222	>2222	>2222

124 nM as the median IC_{90} from either the dual or single cell line

500 nM as cut-off value below which >70% of the isolates are sensitive

Shown in bold are the isolates sensitive to PF-00821,385 at a predicted Cmin of 500nM

- The applicability of the PK-PD-disease model assumptions for gp120 inhibitors was evaluated by applying the approach to publicly available mean data on BMS-488043[3-5].

Simulation

- Viral load-time profiles were simulated in Trial Simulator 2.2 (Pharsight Corp) with different combinations of minimum, mean and maximum values of all PK parameters and low (121 ng/mL) and high (489 ng/mL) IC50 (55 scenarios).
- For each of these scenarios, PF-00821385 was administered Q.D. and B.I.D. at doses ranging from 50 mg to 1300 mg (10 doses) for 10 days;
- Different assumption was made on Ka (½ and ¼) to assess the possibility of controlled release formulations.

RESULTS

PK Analysis

- A total of 969 PF-00821385 concentrations were collected from intensive sampling in 24 volunteers.
- A two-compartment model with first-order absorption and elimination with relative bioavailability fixed to unity was found to be optimal for further model development.
- Inter-individual variability (IIV) was included on the following structural parameters: clearance from the central compartment (CL/F), volume of distribution of the central compartment (V_c/F), and relative bioavailability (F).
- A proportional model was used to describe the residual variability on log-transformed concentration data.
- Parameter estimates and goodness-of-fit plots from the final model are presented in Table 1 and Figure 1 respectively.
- Model provided adequate fit to data although degree of underprediction of Cmax.

Figure 1 Observed Data and Mean Predicted Concentrations

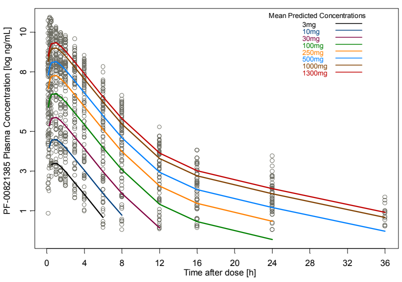
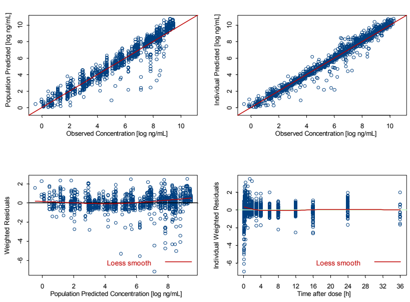


Figure 2 Goodness of Fit Plots for Final PK Model



Simulation

Table 1 Final Model Parameter Estimates, Minimum and Maximum Post Hoc Values, and Inter-Individual Variability Used in Simulations

Parameter	Minimum	Mean	Maximum	IIV (%)
CL/F [L/h]	33.1	35.6	38.0	9.11
V_c/F [L]	5.72	15.8	133	80.4
Q/F [L/h]	-	0.687	-	-
V_p/F [L]	-	6.79	-	-
F	0.362	1 (Fixed)	2.10	37.5
Ka [1/h]	-	0.598	-	-
IC_{50} [ng/mL]	121	-	489	-

Figure 4 Ranges of Possible Decrease in Log_{10} Viral Load For PF-00821385 Administered Q.D. or B.I.D. at Doses from 50 mg to 1300 mg simulated with Ka=0.598 1/h.

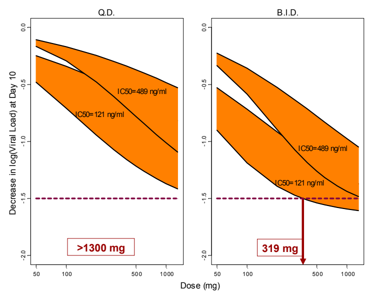


Figure 5 Ranges of Possible Decrease in Log_{10} Viral Load For PF-00821385 Administered B.I.D. at Doses From 50 mg to 1300 mg. Different Ka Values Were Used for Simulation to Examine the Possible Doses Required for Controlled Release Formulation.

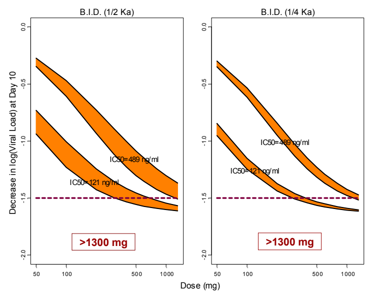
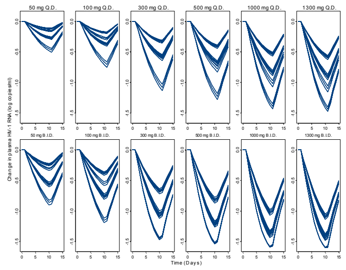


Figure 3 Simulated Viral Load-Time Profiles Following Administration of PF-00821385 at Doses Ranged From 50mg to 1300mg (Q.D or B.I.D.) for 10 Days.



Each profile represents a simulated scenario of any possible combination of PK and PD parameters (19 scenarios).

Table 2 Possible Ranges of Doses of PF-00821385 That are Predicted to Result in a 1.5 log_{10} Decrease in Viral Load.

IC50 (ng/mL)	Ka = 0.598 (1/h)	Dosing	Minimum Dose (mg)	Maximum Dose (mg)
121	Ka	Q.D.	>1300	>1300
	Ka	B.I.D.	319	>1300
	½ Ka	B.I.D.	268	613
	¼ Ka	B.I.D.	250	342
489	Ka	Q.D.	>1300	>1300
	Ka	B.I.D.	>1300	>1300
	½ Ka	B.I.D.	1075	>1300
	¼ Ka	B.I.D.	1006	>1300

CONCLUSIONS

- The plasma PK results showed that PF-00821385 absorption and oral clearance was rapid under fasted conditions.
- The predicted dose required to target 70% of Clade B virus isolates was close to or above the maximum tolerated dose of PF-00821385.
- A controlled release formulation could improve the PK characteristics, but would only be of utility in the treatment of a narrow spectrum of viral sensitivities.
- Further development of PF-00821385 will not be pursued.

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