PK-PD modelling to support go/no go decisions for a novel gp120 inhibitor

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BOS1

Pharmacometrics
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BOS1 – Topic 3

- M&S should be used to make optimal use of all available information including *in vitro*, preclinical (translational M&S), literature and in house data to optimize clinical development and help early selection of safe and efficacious drugs.
- What is the role of M&S in translation from *in vitro*-preclinical data to human?
- Sharing data, database development for translational M&S.
- What are the expectations from Regulators on M&S to support IPoM and PoP/C study design documentation and for their regulatory decision making?
- Is success or failure in early development an internal issue for Pharma companies or is there a role for the regulators?
- How can regulators help Pharma companies make better internal decisions that ultimately result in faster access for patients to safe and effective new medicines?
- What are the standards expected for use and reporting if M&S is used as a platform to compile data and optimize development and candidate drug selection?

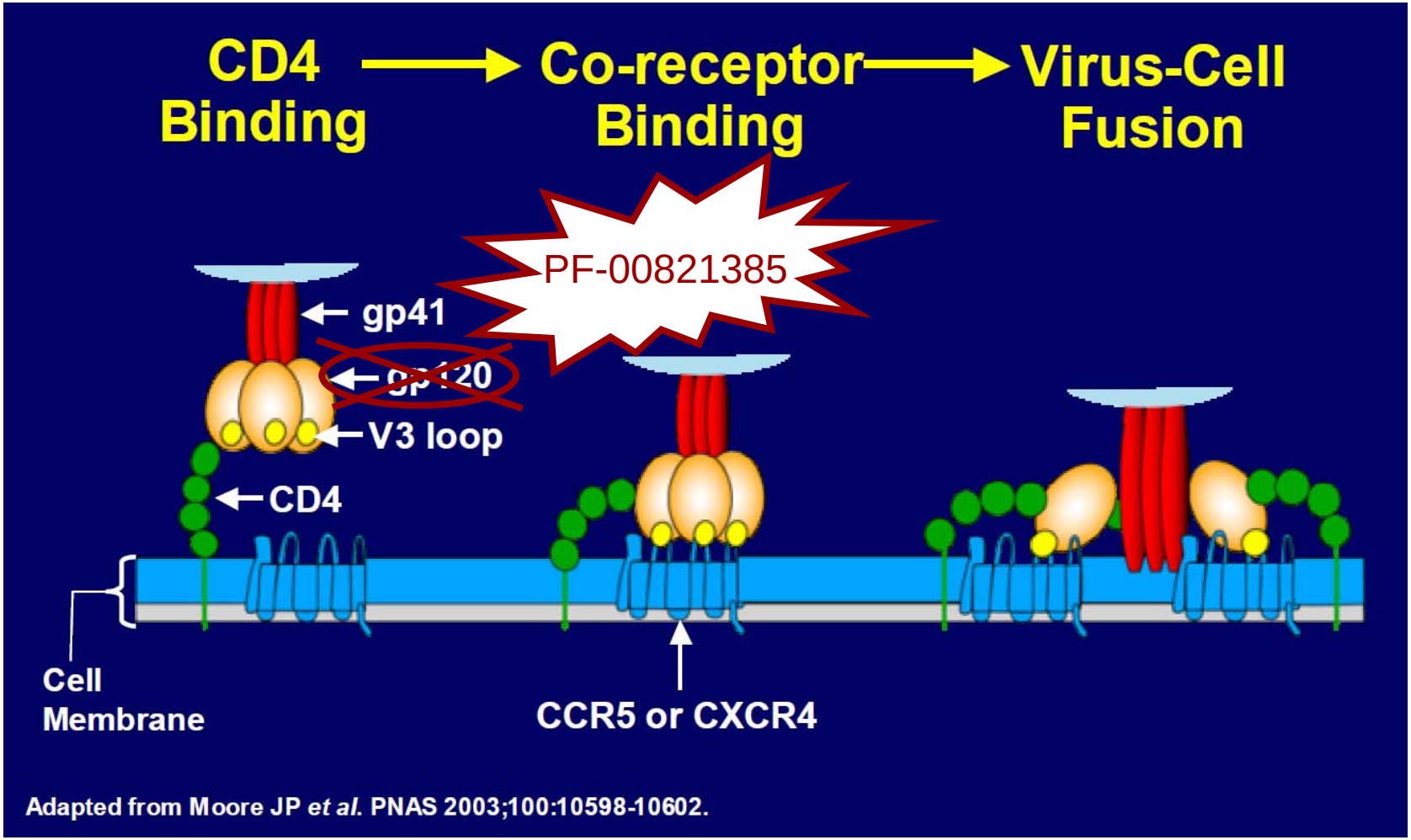
Objective

- To illustrate how PKPD modelling with viral dynamics (VD) model can be used to support HIV drug development decisions
  - Not to pursue further development of PF-00821385

Summary

- Application of PKPD-VD modelling allows
  - Understanding *in vitro* to *in vivo* translation
    - *in vitro* to *in vivo* translation of potency
  - Exploration of study designs
    - Dose size, dosing frequency, formulations
    - Prediction of possible short-term study outcomes
  - Drug development decisions
    - Early termination of project (after FIH)

PF-00821385: Novel Entry Blocker



Activity of PF-00821385 Against Available Clade B Clinical Isolates

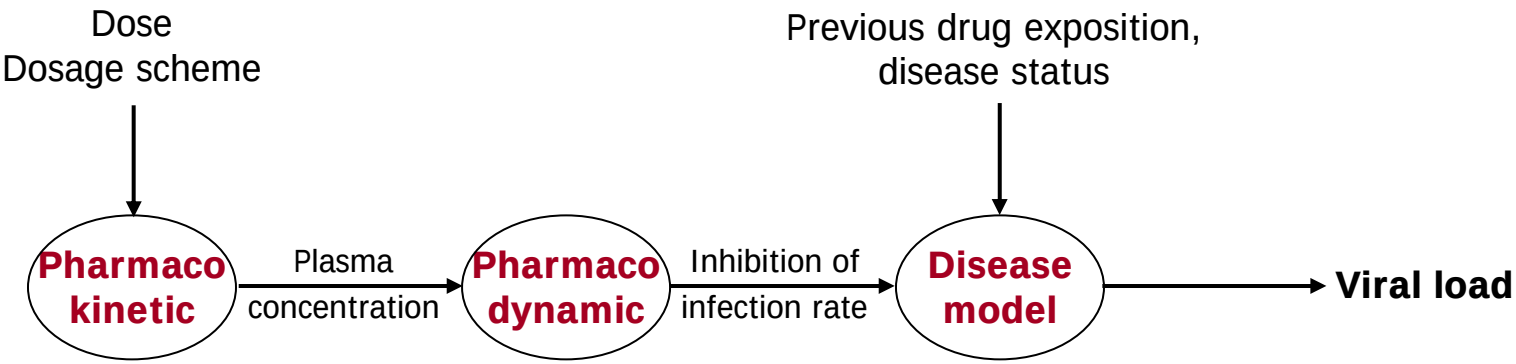
Virus	Tropism	Dual Cell Line		Single Cell Lines	
		IC50 (nM)	IC90 (nM)	IC50 (nM)	IC90 (nM)
04-116871_VL_781.69	R5	2	**12**	2	**9**
04-116884_VL_328.45	R5	2	**13**	2	**9**
04-116877_VL_938.28	R5	4	**18**	4	**21**
04-116873_VL_754.51	R5	4	**22**	4	**21**
04-116868_VL_518.14	R5	5	**21**	5	**26**
04-116870_VL_181.51	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-00821385 at predicted C_{min} of 500 nM

PKPD-VD Model: Developed for Maraviroc[1]



Data source	***-Previous PK studies***	***- In-vitro inhibition of viral turnover***	***- Parameters from literature*** ***- Specific drug data***
Model	***One- or two-compartment First order absorption***	***Emax model***	***Bonhoeffer[2] (adapted)***

[1] *Rosario, et al. Clin Pharmacol Ther 2005;78:508-19*

[2] *Funk et al., JAIDS, 26, 397-404, 2001*

	Round 1: with literature BMS-488043 data	Round 2: with in-house data (prior to FIH study)	Round 3: with in-house data (post FIH study)
Objectives	• Benchmark against competitor compound • To validate previously developed HIV drug-disease model for the class of gp120 antagonists	• To update the PKPD-VD model with PF-00821385 data and predict doses for FIH study	• To update the PKPD-VD model with PF-00821385 **FIH data** and predict doses for FIP study
PK data source	• ***Literature*** available BMS-488043 ➢ mean concentration-time profiles in healthy volunteers ➢ plasma protein binding	• ***Scaled*** PF-00821385 PK parameters from animal data (rat and dog) • PF-00821385 protein binding in human plasma	• Individual concentration-time data from PF-00821385 FIH study
PD data source	• ***Literature*** available BMS-488043 ➢ mean viral load profiles in HIV infected patients (placebo & 2 active doses) ➢ *in vitro* potency	• Median and cut-off IC_{90} in various *in vitro* virology assays • *In vitro* to *in vivo* potency ***translation*** factor from BMS-488043 M&S outcomes	
VD data source	• ***Literature*** and in-house (previous compounds/studies) available HIV viral dynamics model parameters		
M&S outcomes	• Determination of an approximate *in vivo* IC_{50} for BMS-488043 ➢ by comparing the observed and simulated mean viral load profiles • Computation of *in vitro* to *in vivo* potency translation factor	• Prediction of possible range of PF-00821385 doses that result in a 1.5 log_{10} viral load drop for once or twice daily dosing	• Prediction of clinical PF-00821385 doses that result in the targeted 1.5 log_{10} viral load drop for different regimens and formulations

Possible Ranges of Doses of PF-00821385 for a 1.5 $\log_{10}$ Decrease in Viral Load

In Vitro IC_{90} [nM]	Ka = 0.598 [h^{-1}]	Dosing	Minimum Dose [mg]	Maximum Dose [mg]
124	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
500	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

M&S Assumptions

Drug-Disease Model	•Full compliance •No dropout •Drug effect is produced by inhibition of the virus infectivity
M&S with literature BMS-488043 data	•No variability on PK and antiviral potency due to the use of summary level data
M&S with preclinical PF-00821385 data	•Linear PK scaling from animal to human •No variability on antiviral potency with the use of (median and cut-off) *in vitro* IC_{90} values •Same *in vitro* to *in vivo* potency translation factor for both gp120 inhibitors regardless the use of different assays & clinical isolates
M&S with clinical PF-00821385 data	•No difference in PK between healthy subjects and HIV patients •No resistance in naive HIV-1 patients •Targeted 1.5 $\log_{10}$ viral load drop is an accepted criteria for prediction of a good long-term clinical outcome

Discussion Points

What are the views of Regulators on?

1. The use of literature available summary level competitors data to inform / validate / develop drug-disease model in early drug development.
2. The role of M&S in consolidating available information, hypothesis testing and support decision making in early drug development.

Acknowledgements

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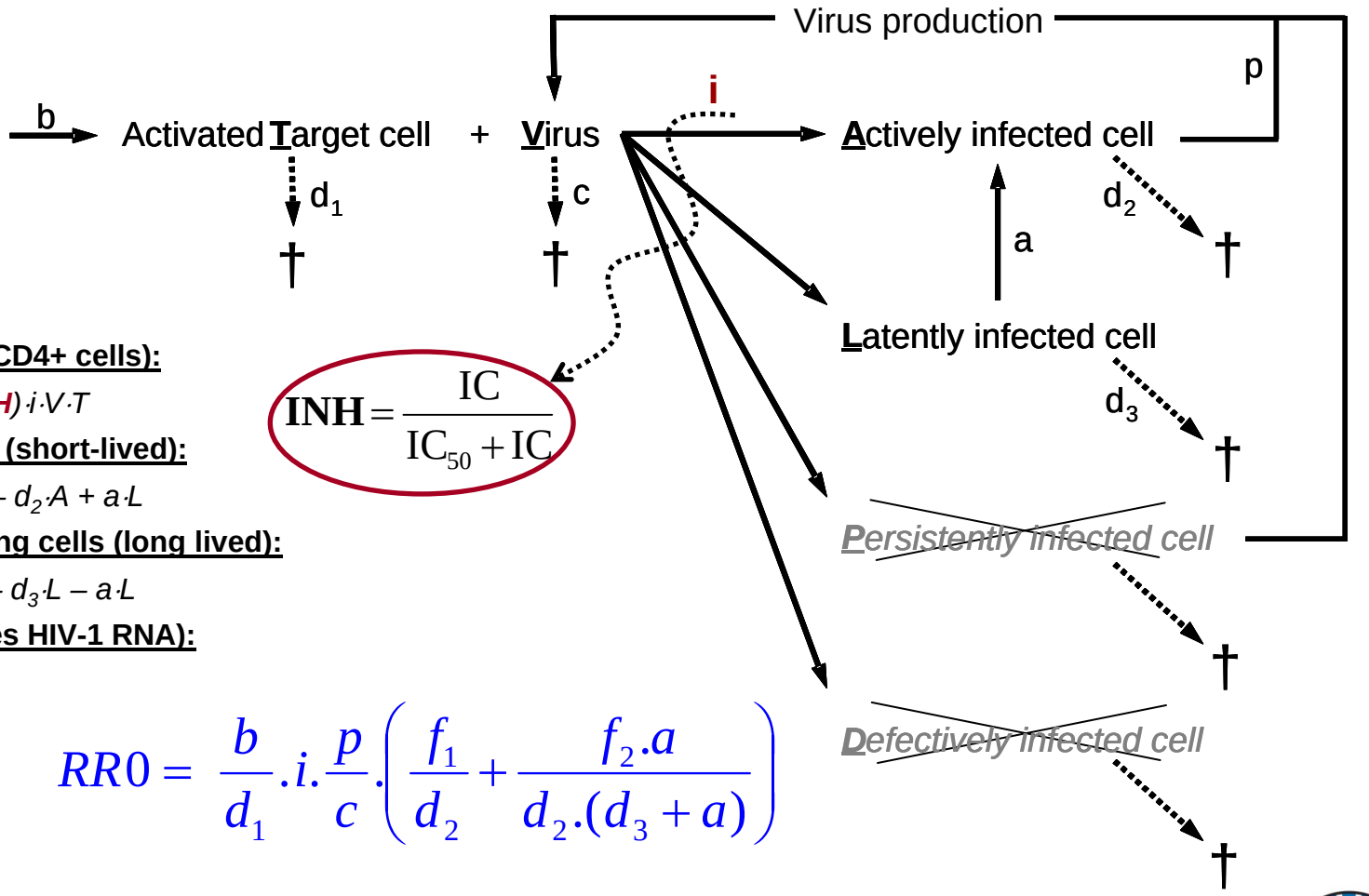
Back-Up

VD Model for HIV
with Inhibitory Emax Model for Drug Effects



Target cell (activated CD4+ cells):

$dT/dt = b - d_1 \cdot T - (1\text{-}INH) \cdot i \cdot V \cdot T$

Actively infected cells (short-lived):

$dA/dt = f_1 \cdot (1\text{-}INH) \cdot i \cdot V \cdot T - d_2 \cdot A + a \cdot L$

Latently infected resting cells (long lived):

$dL/dt = f_2 \cdot (1\text{-}INH) \cdot i \cdot V \cdot T - d_3 \cdot L - a \cdot L$

Infectious virus (copies HIV-1 RNA):

$dV/dt = p.A - C.V$

$$RR0 = \frac{b}{d_1}.i.\frac{p}{c}.\left(\frac{f_1}{d_2} + \frac{f_2.a}{d_2.(d_3 + a)}\right)$$

[1] *Funk et al., JAIDS, 26, 397-404, 2001*

[2] *Rosario, et al. Clin Pharmacol Ther 2005;78:508-19*

Modelling & Simulation Work Prior to FIH Study

Objective: Benchmark against competitor compound to validate the PKPD-VD model for the class of gp120 antagonists

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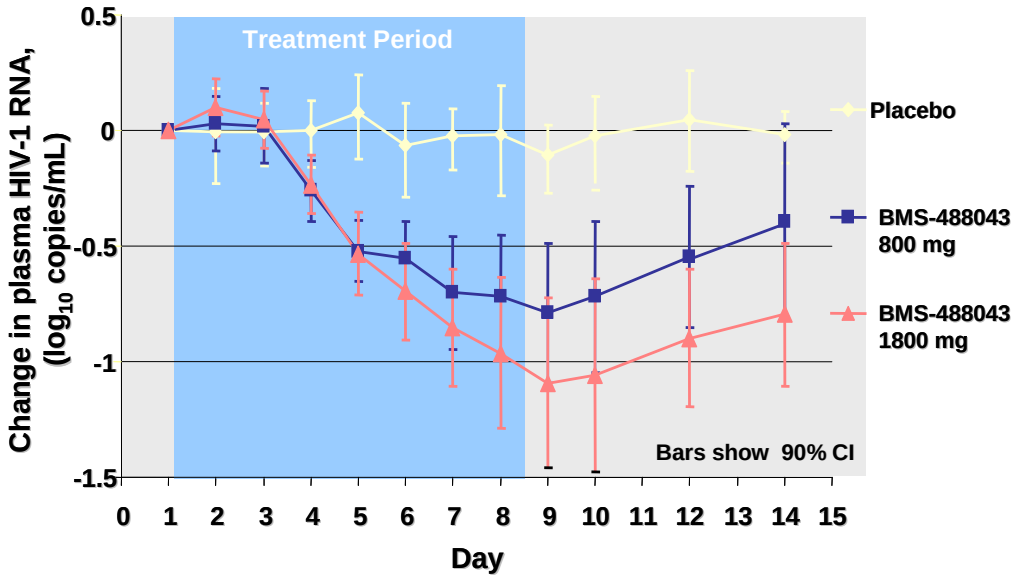
BMS-488043 Available Data

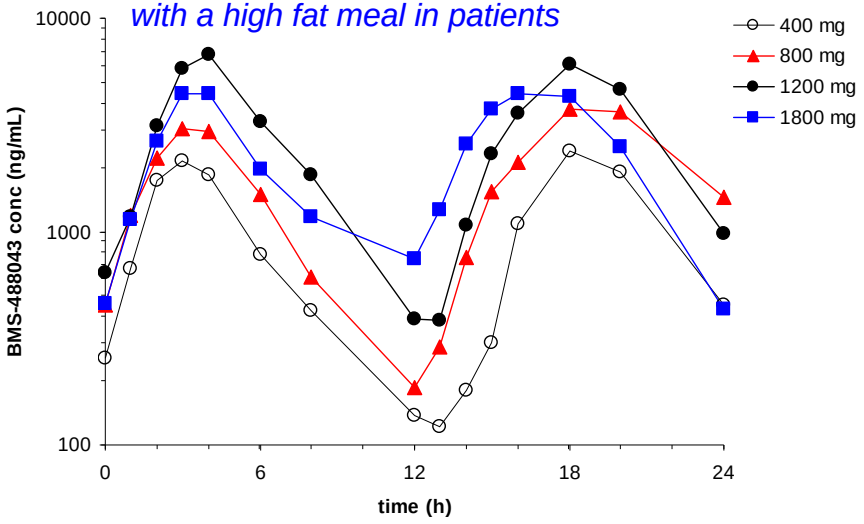
gp120 antagonist in development at BMS

- *In vitro* potency (EC_{50}): median 15 ng/mL (36.5 nM with MW=422), but wide range (1-1000 nM)
- Plasma protein binding: 83.5% *(Lin et al, 2004 CROI, poster #534)*
- Mean concentration and viral load profiles



(Hanna et al., 2004 CROI, poster #141)

800 mg and 1800 mg were administered with a high fat meal in patients

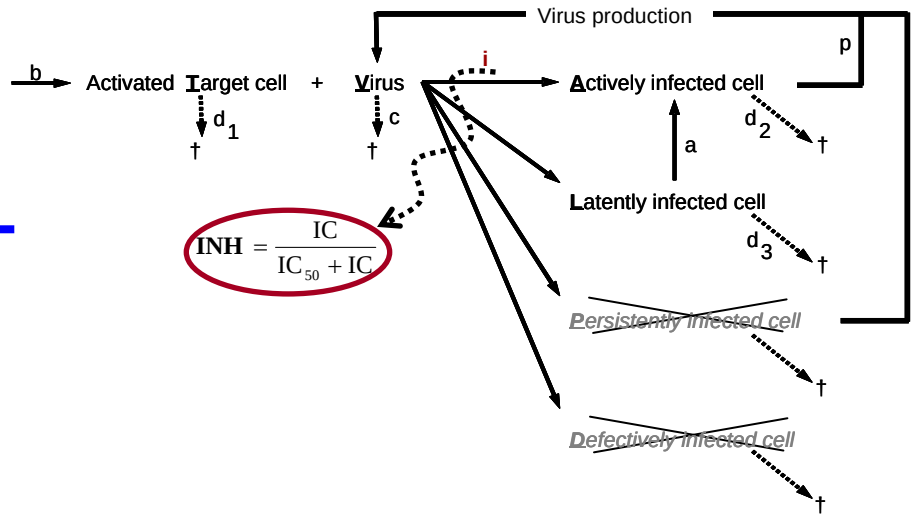


(Hanna *et al., 2004 CROI, poster #535)*

PKPD-VD Simulation for BMS-488043 Based on Mean PK Profiles

Parameter	800 mg dose	1800 mg dose
F2 (relative to F1)	2.39	1.11
ALAG1 (h)	0.545	0.438
ALAG2 (h)	0.452	0.472
D1 (h)	1.72	2.55
D2 (h)	6.33	5.89
Ka1 (h^{-1})	0.395	0.213
Ka2 (h^{-1})	0.279	0.450
V/F (L)	72.5	12.3
CL/F (L/h)	67.2	69.1

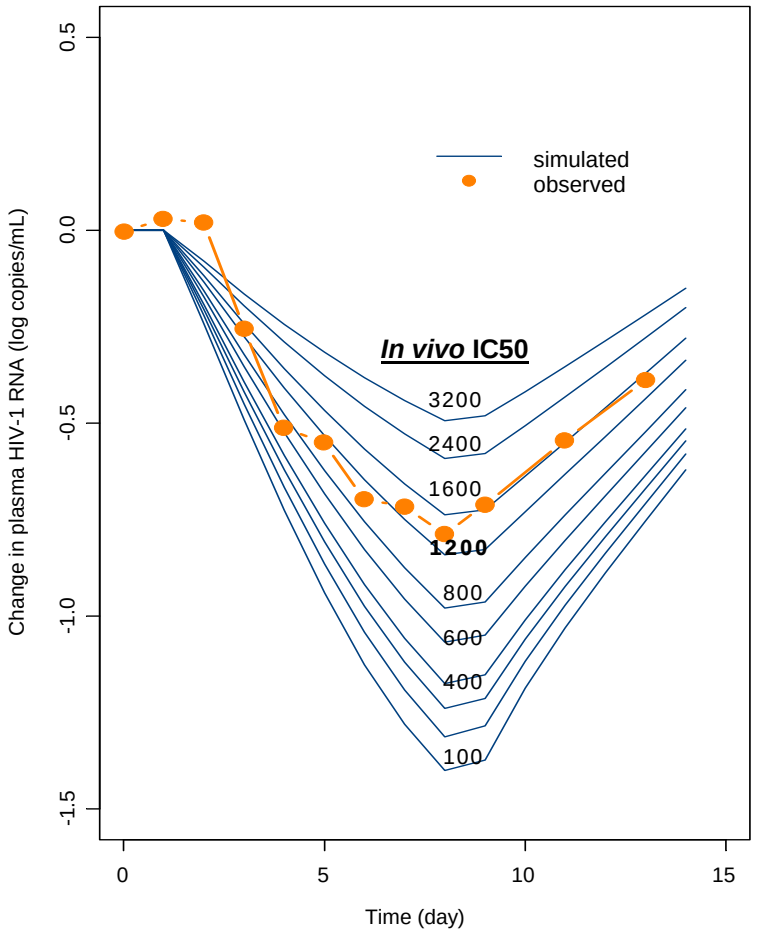
+



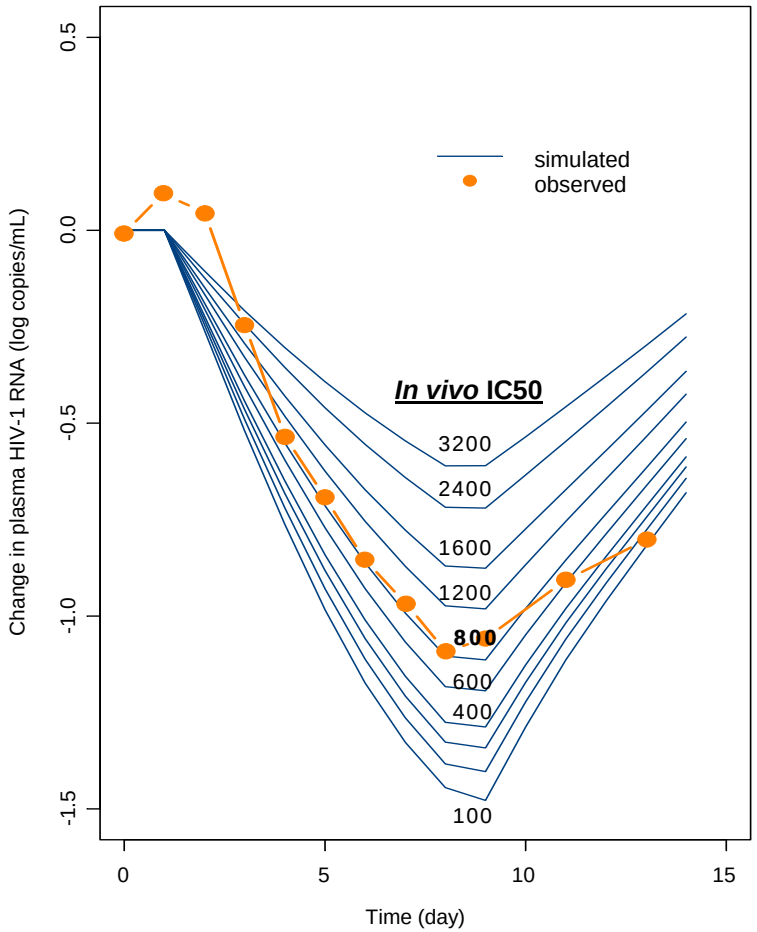
- Treatment: 800 and 1800 mg twice daily for 7 days
- Predicted PK parameters (population analysis using NONMEM)
- Viral dynamics parameters (*Rosario, et al. Clin Pharmacol Ther 2005;78:508-19*)
- Hypothesized IC_{50} range from 100 to 3200 ng/mL

Simulated Viral Load Profiles for BMS-488043

BMS488043 800 mg b.i.d.



BMS488043 1800 mg b.i.d.



Average *in vivo* IC_{50} appears to be approximately 800 to 1200 ng/mL

Modelling & Simulation Work Prior to FIH Study

Objectives: Incorporate animal data for clinical trial simulation to predict FIH doses of PF-00821385

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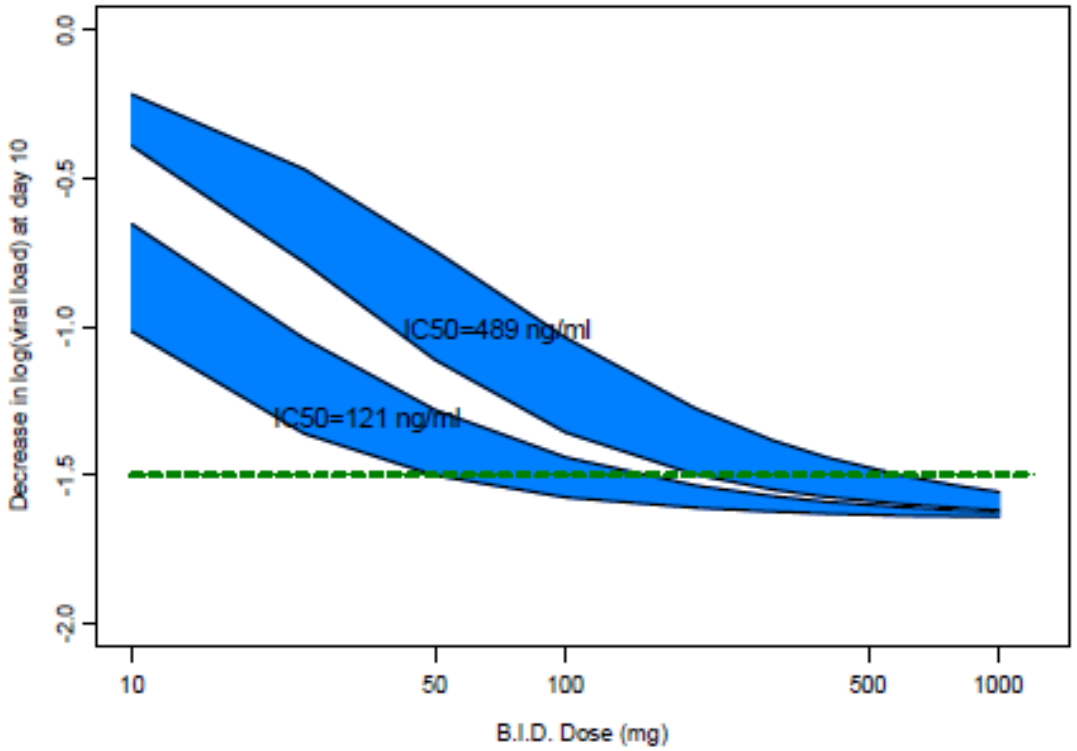
Simulation Scenarios
Scaled PK from Animal to Human

PF-00821385 Q.D. & B.I.D. at doses ranging from 10 mg to 1000 mg for 10 days

Parameter	Minimum	Mean	Maximum
CL [ml/min/kg]	1.3	1.75	2.2
V [L/kg]	0.5	0.75	1
F	0.89	0.915	0.94
Ka (h^{-1})	0.35	0.70	1.40
IC_{50} [ng/mL]	121	-	489

Simulation performed for all possible combination of scaled PK parameter (mean, minimum and maximum) values, and the assumed low and high IC_{50} (162 scenarios)

Ranges of Possible Decrease in Log_{10} Viral Load for PF-00821385 Administered B.I.D. for 10 days at Doses from 10 to 1000 mg

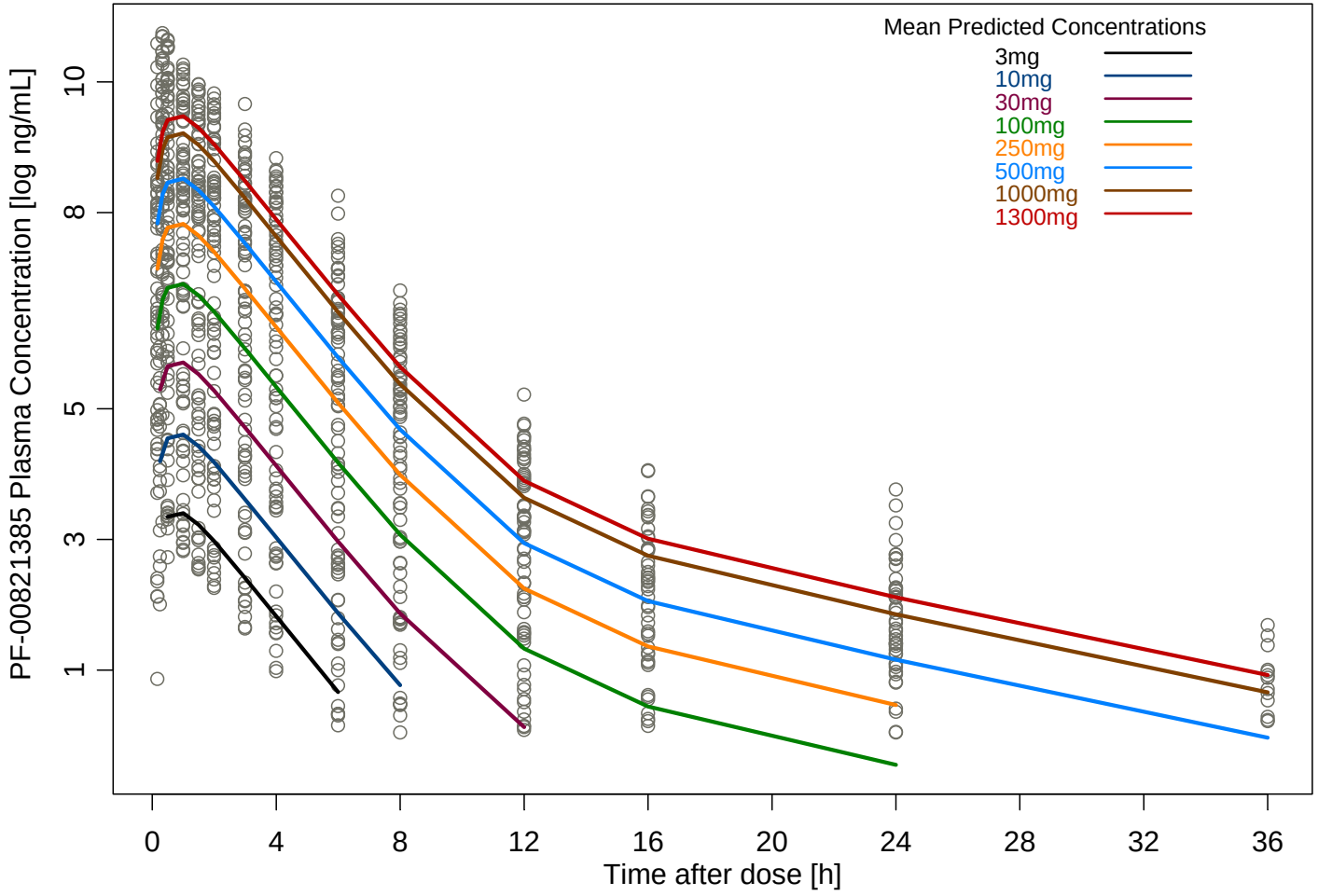


Modelling & Simulation Work
Post FIH Study

Objectives: Incorporate FIH data for clinical trial simulation to predict potential clinical doses of PF-00821385

Observed Data and Population Predicted Concentrations

A total of 969 PF-00821385 concentrations were collected from intensive sampling in 24 healthy volunteers.



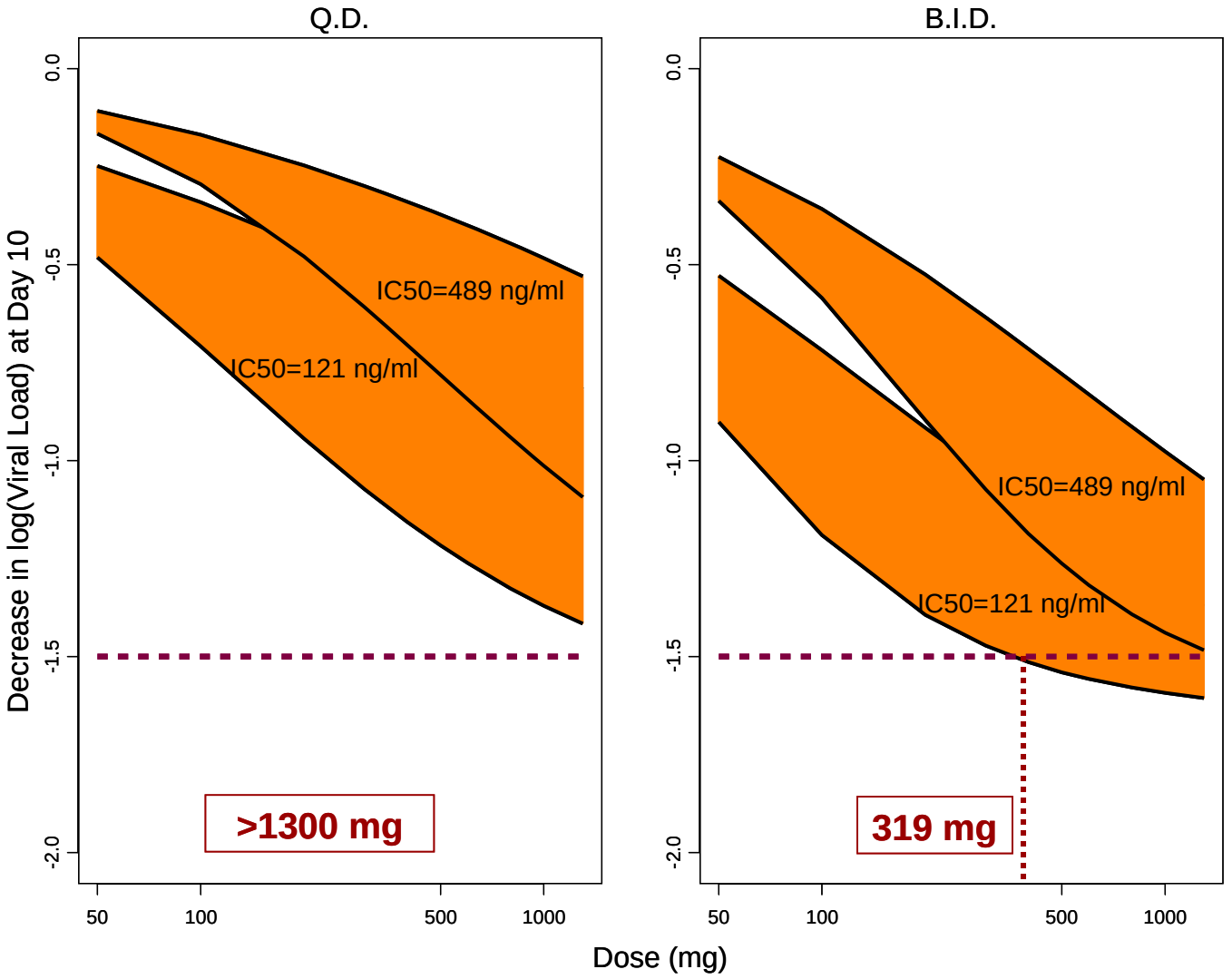
Simulation Scenarios
PK parameters from FIH study

PF-00821385 Q.D. & B.I.D. at doses ranging from 50 mg to 1300 mg for 10 days

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**	**-**

Simulation performed for all possible combination of predicted PK parameter (mean, minimum and maximum *post hoc*) values, and the assumed low and high IC_{50} (54 scenarios)

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



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