Modeling and Simulation of DEBIO-025 to Support Design of a Dose-Response Monotherapy Study in HIV-1 Infected Patients

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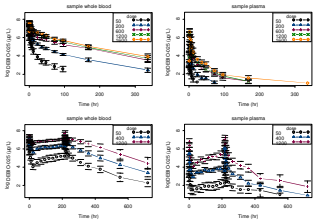
Introduction

- DEBIO-025 is a non-immunosuppressive cyclosporine with potent inhibitory activity on HIV replication *in vitro* due to the inhibition of cyclophilins.
- A new study to refine dosing regimen and better assess dose-response (study 103) is planned.
- The goal of this project was to help assess the dosing regimen with maximum efficacy on HIV replication and to recommend design for the next study. The specific objectives include:
  - Develop a longitudinal drug-disease pharmacokinetic-pharmacodynamic ("PK/PD") model that describes the relationships among dose, exposure, and viral load in patients with HIV-1 infection.
  - Simulate dose-response and optimal dosing regimen in HIV-1 infected patients.
  - Simulate designs for the next study.

Data

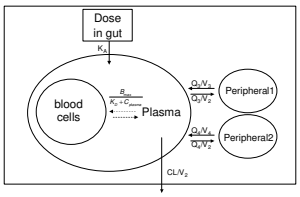
- Phase I in healthy volunteers (study 101)
  - Single-doses of 50 to 1600 mg
  - 16 subjects
  - Well tolerated
  - PK data in plasma and whole blood
- Phase I in HIV-1 infected subjects (study 102)
  - 10 days treatment at 50, 400, 1200 mg once a day
  - 29 patients
  - PK data in plasma and whole blood
  - Viral load data

Pharmacokinetic Data: Study 101 and 102

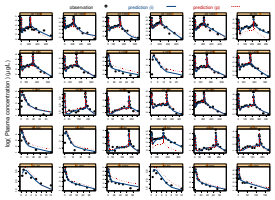


The concentrations in blood cells were calculated for each patients based on hematocrit.

Pharmacokinetic Model



Plasma profiles are well captured by the 3-compartment pop PK model, both on the population as well as on the individual level



Parameter estimates 1: Fixed effects (CV in %) 3-compartment model provided the best fit

	2 compartments	3 compartments
Objective function	28048	27750 (- 297)
K_a (h-1)	1.46 (5.8)	1.21 (6.0)
CL (L/h)	163 (4.8)	157 (4.9)
V_c (L)	1010 (5.9)	915 (5.3)
Q_p (L/h)	171 (6.3)	162 (6.9)
V_p (L)	6350 (6.2)	3420 (9.7)
Q_d (L/h)	-	45.8 (17.3)
V_d (L)	-	8800 (14.7)
B_{base} (µ/L)	2950 (2.9)	3050 (3.0)
K_D (µ/L)	43.1 (4.8)	45.4 (4.8)
K_{on} / K_{off} (h-1)	0.169 / 0.0269	0.177 / 0.0474
K_{on} / K_{off} (h-1)	-	0.0501 / 0.0052
K_{in} (h-1)	0.161	0.172
$t_{1/2,\,Ld}$ (h)	55.0 (2.3 days)	177.3 (7.3 days)

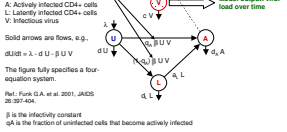
Parameter estimates 2: Random effects (CV in %)

	2 compartments	3 compartments
ω_{K_a} (%)	34.1 (22.3)	40.0 (22.1)
ω_{V_c} (%)	31.4 (29.3)	30.9 (22.5)
ω_{CL} (%)	32.3 (32.7)	33.2 (31.1)*
ω_{V_d} (%)	-	96.0 (18.9)
$\omega_{B_{base}}$ (%)	14.9 (16.9)	14.4 (16.8)
ω_{Plasma} (%)**	39.5 (4.3)	36.5 (5.4)
$\omega_{Blood\ cells}$ (%)**	22.3 (5.7)	21.3 (6.6)

* ω_{CL} random effect on Q_p instead of V_d
** residual variability includes inter-occasion variability

HIV drug-disease model links continuous-time PK, viral inhibition, and viral dynamics sub-models

- For each patient, the PK model predicts concentrations over time C(t).
- Viral inhibition is the fraction I(t) = C(t) / (C(t)+IC50).
- One minus the inhibition fraction multiplies (reduces) an infectivity constant in the viral dynamics model:

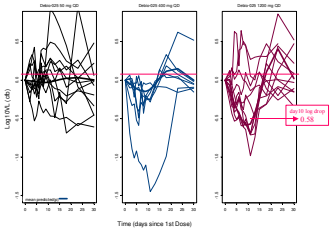


Viral Load Model Parameter estimates

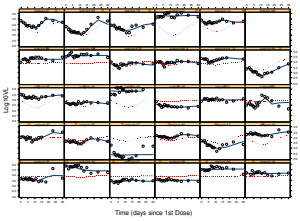
Parameter	Estimate (CV %)
R0 (no units)	7.00 (fixed)
λ (cells/µL/day)	0.14 (19%)
d_A (1/day)	0.54 (39%)
IC_{50} (µg/mL)	0.43 (100%)
Variability:	
SD of ln(R_0) (%)	83% (618%)
SD of ln(λ) (%)	79% (294%)
SD of ln(d_A) (%)	79% (299%)
SD of ln(IC_{50}) (%)	171% (67%)
SD of residual for log10(viral load) (log10 copies/mL)	0.16 (35%)

R0 reproductive ratio
λ birth rate of uninfected cells
d_A death rate constant actively infected cells
IC_{50} inhibition constant

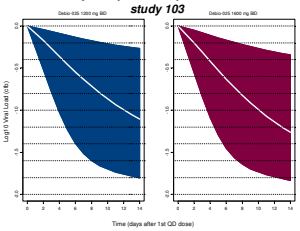
Mean population predicted log drop (change from baseline in viral load) adequately describes the observed data



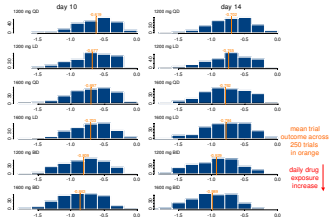
The individual patient data are well described by the model



Model simulations (90 % prediction interval) indicates great uncertainty in expected response. Hence the value of study 103



Distribution of trial outcomes (mean log10 drop) from 250 trials with 18 drug-treated patients



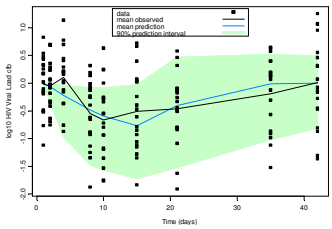
Regimens for trial 103 have moderate to high probability of achieving relevant efficacy endpoints

Day 14	1200 mg QD	1600 mg QD	1200 mg LD	1600 mg LD	1200 mg BID	1600 mg BID
Pr(>0.5 log drop)	0.73	0.78	0.74	0.79	0.88	0.94
Pr(>0.8 log drop)	0.36	0.48	0.38	0.46	0.62	0.68
Pr(>1.0 log drop)	0.17	0.27	0.22	0.26	0.40	0.48

LD stands for loading dose which was 2days of 1200mg BID followed by 1200mg or 1600mg QD.

The team elected to use a 1200 mg b.i.d. regimen for study 103

Model predictions vs. Study 103 actual results (1200 mg b.i.d. for 14 days)



Conclusions

- A M&S framework was developed to support the development of DEBIO-025 and helped the project team to make decisions regarding the design of the next study.
- Drug exposure is an important determinant of response but other factors (i.e. related to the host and the virus) need to be identified.
- Simulations were performed to evaluate the expected clinical response for a typical patient (population mean) and in single arm 18-patient clinical trials.
- The models and simulations summarized the current understanding of DEBIO-025's anti-HIV response in monotherapy, given the data that were available.
- Simulations were based on extrapolations and there was a large uncertainty in the expected antiviral response.
- In study 103:
  - Drug exposure was higher than predicted by the PK model (not shown).
  - Viral load data were consistent with model predictions.