Physiologically Based Pharmacokinetic (PBPK) Modelling: Applications in Drug Discovery

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PBPK models are invaluable tools for enabling decision making in drug discovery and development. When a PBPK model is developed and validated for a clinical candidate, it can help in simulating "what-if" scenarios such as predicting clinical drug-drug interactions based on preclinical data. Such simulations provide a rational basis for understanding the candidate's potential for co-administration with drugs which are either substrates, inhibitors or inducers of drug metabolizing enzymes. This is illustrated by a case study with Pracinostat.

Pracinostat: *In vitro* CYP450 data

CYP450	CYP450 Isoform Typing Metabolic stability (rhP450), Cl_{int} (µl/min/pmol CYP450)	CYP450 inhibition IC_{50} (µM) (Mean +/- SD)	CYP450 Induction Fold Induction Positive control (%)
CYP1A2	0.89	>25	31.8 (Omeprazole)
CYP2C9	stable	>25	NA
CYP2C19	stable	5.8 +/- 5.9	NA
CYP2D6	stable	>25	NA
CYP3A4	0.18	>25	13.8 (Rifampicin) 18 (Dexamethasone)

1. Will PK of Pracinostat be affected by CYP3A inhibitors?

1. Will PK of Pracinostat be affected by CYP3A inducers?

2. Will Pracinostat affect the PK of Omeprazole?

PBPK Model for Pracinostat

Pracinostat data

Parameter	Value
Mol Weight (g/mol)	358.48
log P	2.39
Compound Type	Diprotic Base
pKa 1	7.45
pKa 2	4.13
B/P	1.0
f_u	0.082
f_u(Gut)	1.0
Enzyme	CYP1A2
CL_{int} (µL/min/pmol isoform)	0.894
$f_{u\ mic}$	0.34 (Turner)
Enzyme	CYP3A4
CL_{int} (µL/min/pmol isoform)	0.180
$f_{u\ mic}$	0.34

System

Healthy Human volunteer population (10 subjects /trial; total subjects =100).

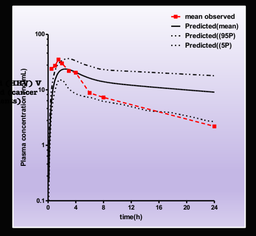
PBPK Model

- **Simcyp (9.3)**
- **Assumptions**

1) major plasma binding protein : 1 acid glycoprotein (SB939 – weak base)
2) fraction unbound in enterocytes (f_g) =1
3) metabolism main clearance mechanism

- **Absorption - ADAM model**
- **Formulation – IR**
- **Physiologically based distribution model (method 2, basic pKa of SB939 =7.0).**
- **Elimination- recombinant enzyme (CYP3A4, 1A2)**

Single oral dose 10 mg (FTIH dose) administered to population



FTIH dose

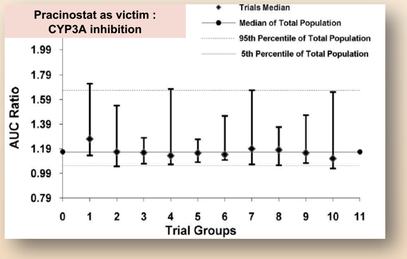
Parameter	Predicted Mean (5-95% Percentile) N=100 healthy subjects)	Observed (Mean, Range) N=3 patients
AUC (ng.h/ml)	316 (141-523)	229 (171-275)
T_{max}(h)	2.6 (1.6-3.5)	1.8 (0.5-4)
C_{max} (ng/ml)	25 (17-37)	39 (27-58)
CL/F(l/h)	37 (19-71)	39 (27-58)

Recommended dose

Parameter	Predicted (Mean, 5-95% Percentile) N=100 healthy subjects)	Observed (Mean, Range) N=6 patients
AUC (ng.h/ml)	1899 (848-3166)	1152 (711-1945)
T_{max}(h)	2.7 (1.5-3.4)	1.8 (1.0-3.0)
C_{max} (ng/ml)	148 (98-220)	178 (73-320)
CL/F(l/h)	37 (19-71)	59 (31-84)

Simulate with PBPK Model

Ketoconazole (inhibitor) dosed at 400 mg q.d.,4 days; Pracinostat given as single oral dose of 60 mg (RD) on 4th day with Ketoconazole

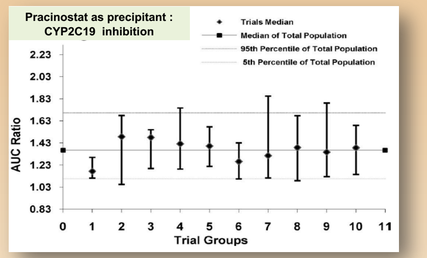


Pracinostat PK weakly affected by Ketoconazole (AUC ratio < 2)

Rifampicin dosed at 600 mg q.d.,5 days, followed by a single 60-mg dose of Pracinostat on 5th day with rifampicin

Pracinostat PK weakly affected by Rifampicin (AUC ratio > 0.5)

Pracinostat dosed at 60 mg q.d. every other day for 1 week (3 doses), followed by a single oral dose of omeprazole (20 mg) with last dose of Pracinostat



Omeprazole PK weakly affected by Pracinostat (AUC ratio < 2)

Reference: : Jayaraman et al. 2011. Drug Metab Dispos. 39(12):2219-3.