Population PK/PD Modeling of a Hepatitis C NS3 Inhibitor

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Kinesis
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Introduction

ACH-0141625, currently undergoing phase II clinical testing, is an inhibitor of HCV NS3 protease with promising intermediate results. Earlier pharmacokinetic studies showed a high variability in PK and investigation was needed to see if a proposed dosing regimen of 200 mg QD FED would be sufficient to meet its *in vitro* target inhibition concentration, especially in case the compound is not taken as directed.

Objectives

- To colligate observed PK to viral load and to obtain insight in the ACH-0141625 viral inhibition profile;
- To use this inhibition profile to simulate anti-viral activity for several candidate dosing regimen (including a loading dose);
- To obtain *in vivo* target concentrations, corresponding to 50% and 90% viral inhibition (EC_{50} and EC_{90} respectively);
- To obtain exposure percentiles for the proposed dosing regimen.

Study Design

- Escalating single dose (SD) segment to assess safety and tolerability, followed by various multiple dosing segments.
- SD segment is excluded in the model due to different profiles and because it dealt with doses outside the interval of interest.

Dose (mg)	QD, BID	Fed, Fasted	HV, P*
600	BID	Fed	HV
1000	BID	Fed	HV
600	BID	Fed	P
500	BID	Fed	P
200	BID	Fed	P
600	QD	Fed	P
600	QD	Fasted	P
400	QD	Fasted	P

* HV = Healthy Volunteer; P = Patient

PK model

Bioavailability

- Geometric mean of dose normalized AUC's about 4 times higher for single dose FED intakes compared to FASTED intakes (NC analysis);
- Bioavailability for subsequent intakes increase 6-fold for FED and 3-fold for FASTED. (NC analysis);
- ACH-0141625 interacts with GI efflux transporters.

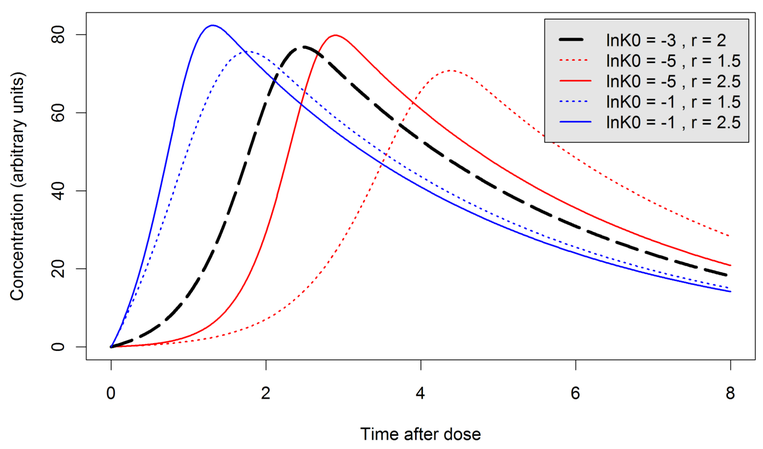
Absorption

- First order absorption could not describe relatively fast decline in concentrations after T_{max} as seen in PK data;
- NONMEM 6 had difficulties estimating variability on standard PK parameter ALAG1;

Therefore, a time dependent first order absorption rate constant was used: $k_a(t) = e^{\ln k_0 + rt}$, with *t* representing time after last dose.

Note that *r = 0* implies a standard first order absorption rate constant.

Flexibility of Absorption



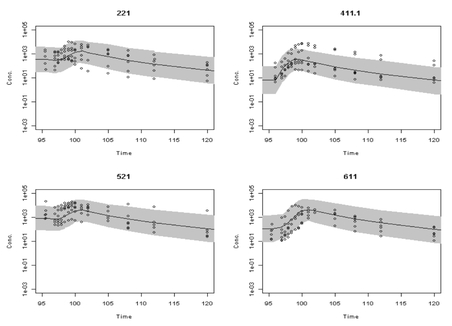
- A lag time can be achieved by lowering ln k_0, see red lines in graph above;
- Faster decline in concentrations after T_{max} can be achieved by increasing *r*, see solid red and blue lines.

PK model

- Three compartments, with the two peripheral compartments having equal *V*;
- Time dependent absorption rate constants; different ln k_0 for fed and fasted;
- Different bioavailabilities for fed/fasted and first/subsequent intakes;
- Inter-individual variability on *F*, ln k_0, clearance (CL) and V_c.
- A '`BLOCK`' was used on *F*, CL and V_c to allow for correlations.
- Due to the large intra-individual variability, the data were fitted after log tranformation, implying $DV_{ij} = IPRED_{ij} \bullet \exp(\varepsilon_{ij})$.

Estimation

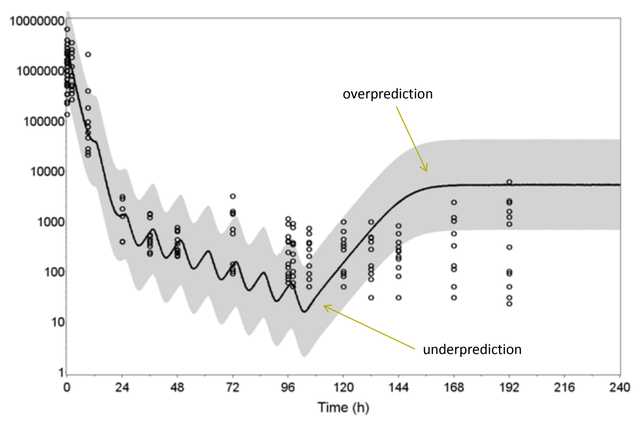
- '`FOCE INTER`' in NONMEM v6;
- Structural parameters could be estimated well: CV < 44%; OMEGA's < 27%;
- Shrinkage <= 11%



HCV model

Viral inhibition was linked to individual PK curves using an HCV model as described by Neumann et al. [1].

Initially, viral inhibition efficacy ε was implemented by a sigmoidal function of plasma concentration *C*. However, this could not describe the compounds prolonged effect correctly, as can be seen in the VPC on the right.



Adapting the Neumann model for hysteresis

To be able to describe the prolonged effect, the viral inhibition was linked to an effect compartment:

$$\varepsilon(C_{ec}) = C_{ec} / (EC_{50} + C_{ec}).$$

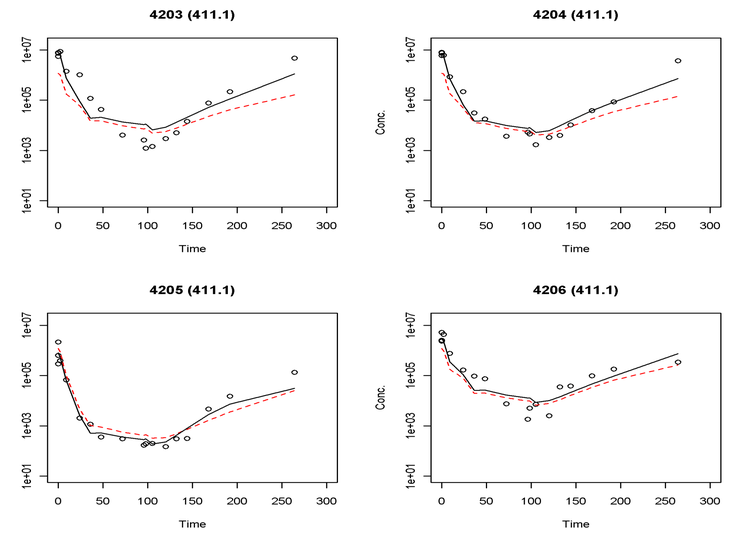
This improved MVOF by more than 200 pts. The dynamics of the adapted Neumann model are thefore:

	Description	Dynamics
T	No. of target cells	$dT/dt = s - dT - (1-\eta)\,\beta VT$
I	No. of infected cells	$dI/dt = (1-\eta)\,\beta VT - \delta I$
V	Viral load	$dV/dt = [1 - C_{ec} / (EC_{50} + C_{ec})]\,pI - cV$
C_{ec}	Concentration in effect compartment	$dC_{ec}/dt = K_{eo} \bullet (C - C_{ec})$

Estimates for EC_{50}† and K_{eo}

K_{eo} = 0.0473 meaning $T_{1/2,\,Keo}$ is about 14.7 hours.
The effect-site equilibrium delay rate constant implied that steady state at the site of action will be reached in about 3 days.

Individual fits are adequate and the prolonged effect is described well (last intake at Time = 96 hrs). Furthermore, the bias as seen in the VPC on the left has disappeared – see graphs below.



FOCE resulted in rounding errors, so method FO was used instead.

Parameter Tables

PK model parameters	Estimate	Std. error	Ω (Shrinkage)
ln k0	-6.67	0.787	2.45 (11%)
Δln k0 fasted	2.93	0.564	
R	1.96	0.464	
ln F fed/MD	1.87	0.17	3.86 (7%)
ln F fasted/MD	-0.299	0.213	
ln F (SD)	-1.39	FIX (1)	
Clearance	139	26.3	1.72 (10%)
Vcentral	532	113	2.42 (10%)
Q(P1)	1.26	0.365	
Vperiph	49.9	21.9	
Q(P2)	7.51	3.21	
σ^2	0.597	0.0874	

(1) Fixed to value from NCA for stability

Ω Block	Vc	F
CL	1.97 (9%)	2.28 (9%)
Vc		2.73 (8%)

PD model parameters	Esti-mate	Std. error	Ω
EC50	(†)	0.0606	1.7
δ	0.0088	FIX (2)	
C	0.311	0.0177	
Prod	2.26	0.579	1.22
ln β	-18.8	FIX (2)	
Sh	1480	FIX (2)	
ln D	-8.52	FIX (2)	
Keo	0.0473	0.00279	0.263
σ^2	0.537	0.0822	

(2) Certain HCV parameters were hard to estimate and therefore fixed to the geometric mean of values found in Dahari et al. [2].

Conclusions and Discussion

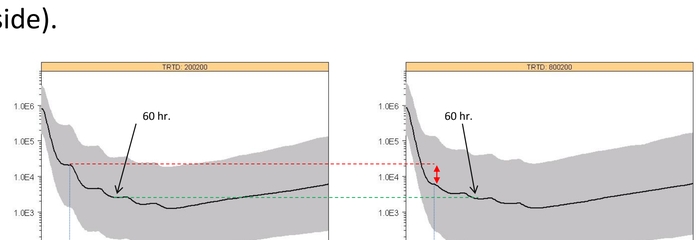
Significant food and MD effect

- Bioavailability (F) increases with MD intakes;
- Food effect on F different for SD and MD, due to ACH-0141625 binding to transporters in the gut.

Relative F	1st intake	Subsequent intakes
Fed	1	6.5
Fasted	0.25	0.74

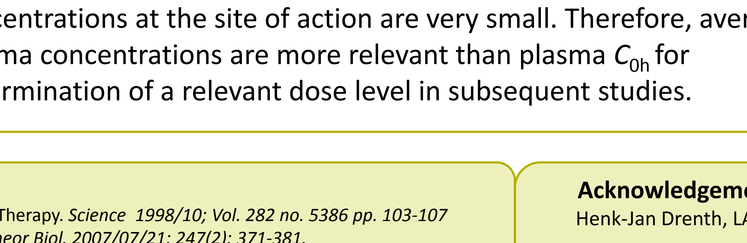
Loading dose proved not necessary

PK/PD simulations showed no benefit in a quadruple loading dose, see graph below. The predicted effect on viral load after 60 hours is negligible (loading dose shown on the right hand side).



Quantiles

In the graphs on the right, the predicted concentration quantiles (green: median; blue: 25%; red: 10%; black: 5%) for day 15 of a 200 mg QD regimen are displayed over time. Horizontal lines EC_{50} (solid); EC_{90} (dotted).



Below are the percentages of patients with trough concentrations meeting EC_{50} and EC_{90} concentrations at the effect site after 15 days dosing. (In brackets are the fractions meeting EC_{50} and EC_{90} concentrations in plasma).

Target	200 mg QD	200 mg QD + accidental fasted	200 mg QD fasted
EC_{50}†	100% (99.9%)	100% (97.2%)	100% (93.5%)
EC_{90}†	100% (93.1%)	100% (69%)	98.4% (50.7%)

Discussion

Effect site concentrations proved more important than plasma concentrations. Due to the large amount of hysteresis, fluctuations in concentrations at the site of action are very small. Therefore, average plasma concentrations are more relevant than plasma C_{0h} for determination of a relevant dose level in subsequent studies.

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References

[1] Neumann, A.U., Lam, et al. - Hepatitis C Viral Dynamics in Vivo and the Antiviral Efficacy of Interferon-α Therapy. *Science 1998/10; Vol. 282 no. 5386 pp. 103-107*
[2] Dahari, H. et al., - Modeling hepatitis C virusdynamics: Liver regeneration and critical drug efficiency. *J Theor Biol. 2007/07/21; 247(2): 371-381.*

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† Values of EC_{50} / EC_{90} obfuscated on request of sponsor.