An HCV nucleoside inhibitor MK-3682 minimal PBPK-PD model for application in hypothesis generation regarding metabolic pathways and perturbations under various conditions

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Introduction

MK-3682 is a uridine nucleoside monophosphate prodrug inhibitor of HCV NS5B RNA polymerase. Following metabolism of MK-3682, it is activated by phosphorylation to form the pharmacologically active nucleoside triphosphate (NTP). NTP, in this context, is the collective term for UTP (uridine triphosphate) and CTP (cytidine triphosphate). NTP does not circulate in plasma and direct measurement of liver NTP levels is technically not feasible in early clinical development. A direct link between NTP concentration and efficacy therefore cannot be established. Given the hypothesized metabolic pathway (see Figure 1), the pharmacokinetics of MK-3682 and its metabolites may contain important information for the link between MK-3682 dose and NTP concentrations at the effect site.

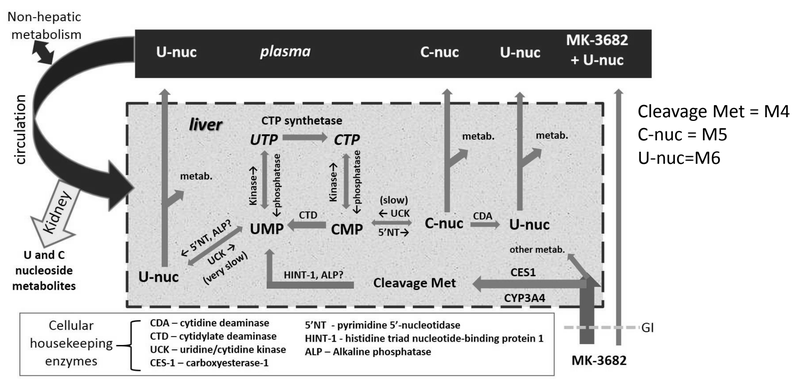

Figure 1 Anticipated metabolism by host (human) housekeeping enzymes

Objectives

The objectives of this work were to:

- Support the understanding of the metabolism of MK-3682
- Predict liver NTP concentrations and link those to efficacy
- Investigate the impact of various intrinsic and extrinsic factors:
  - Formulation (tablet, capsule, IV)
  - DDI with CYP3A4/P-gp perpetrator itraconazole
  - Subject status (healthy volunteers or HCV patients)

Methods

A minimal PBPK model approach, based on Brill et al [1], was applied to characterize the PK of MK-3682 and its metabolism to M5 and M6 in both the gut wall and the liver. The minimal PBPK model was developed in a stepwise approach.

Step 1: Establish the base structure of the model using IV and tablet data after MK-3682 monotherapy in healthy volunteers

Step 2: Investigate the influence of formulation, HCV status and itraconazole coadministration on the PK of MK-3682, M5 and M6

Step 3: Investigate the link between the projected NTP and viral load (VL) by using the individual *posthoc* parameters from the PK model

The model was developed using the non-linear mixed-effects modelling software NONMEM V7.2.0 [2] and data processing was done using R [3] and RStudio [4].

Data

PK data from five phase I studies and one phase I/IIa study were used (n=217 unique subjects). The dataset encompassed data from:

- IV or oral (capsule or tablet) formulations
- Healthy volunteers and HCV patients
- MK-3682 administered alone or in combination with the strong CYP3A4/P-gp inhibitor itraconazole (in HV and HCV patients)
- Doses ranging from 50-750 mg given as single and multiple doses

In the table below the included data for Step 1 and Step 2 of the analysis is summarized. For Step 3 of the analysis, efficacy data from all HCV patients in step 2 (88) were included.

Step 1

Formulation	Dose (mg)	Subject Status	Treatment	N*
IV	25	HV	Alone	14
Tablet	150-750	HV	Alone	100

Step 2

Formulation	Dose (mg)	Subject Status	Treatment	N*
Capsule	50-300	HV	Alone	47
Tablet	300-450	HCV	Alone	16
Capsule	50-400	HCV	Alone	64
Tablet	300	HV	Itra DDI	11
Tablet	300	HCV	Itra DDI	8

* N displays the number of individual curves, which due to cross-over design of some studies, does not sum up to 217.

Model

The model included compartments for (Figure 2):

- Gut wall, portal vein and liver
- MK-3682 (parent)
- Formation pathways in gut and liver for M5 and M6
- UXP and CXP (NTP pool for link to Viral Load)

Co-adminstration with itraconazole resulted in lower initial M5 and M6 concentrations, whereas the effect on viral load was increased. The model estimated gut extraction was significantly lower in the presence of itraconazole, resulting in:

- Higher MK-3682 concentrations
- Faster increase in UXP + CXP concentrations
- Faster onset and slower washout of effect (VL)

It was particularly important to separate the pathways that included the NTP pool and those omitting the NTP pool (i.e. direct M5 and M6 formation in gut), as only M5 and M6 formed in liver are derivatives of NTP, which drives the effect.

Important features of the model:

- Observed less than dose proportional PK of M6 after oral dosing described with concentration-dependent gut uptake
  - M5 and MK-3682 were dose linear
- M5 gut formation rate required to describe PK after oral dosing
- Pseudo-M4 gut route required to fit IV and oral data simultaneously
- Concentration dependent rate from UXP to CXP required to describe single and multiple dose data simultaneously

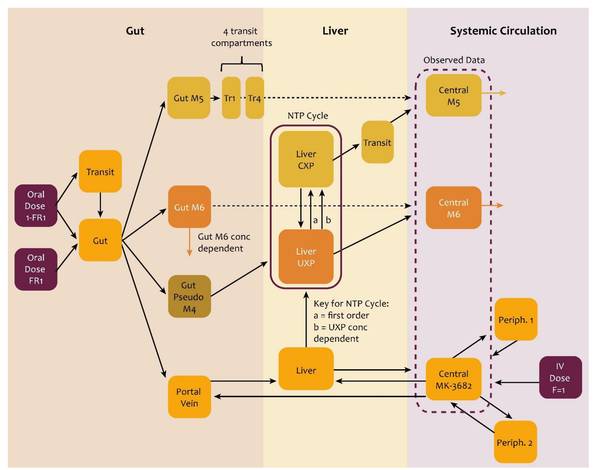

Figure 2 Schematic PBPK model for MK-3682

Results

Key model features that can be observed in Figure 3:

- Double absorption peak (direct and via transit) MK-3682 predicted
- PK of MK-3682 and M5 were dose proportional
- PK for M6 was less than dose proportional due to the saturable M6 gut formation pathway

Key model features that can be observed in Figure 4:

- HCV status has only impact on M5 PK
- Concentrations of M5, M6 and UXP are initially higher for the capsule formulation
- M5 and M6 concentrations are initially lower in the presence of itraconazole, whereas UXP concentrations are higher. The higher UXP concentrations explain the faster onset and slower washout of the effect in the presence of itraconazole (see Figure 5, in which epsilon is the effect parameter of the sigmoid Emax function in the KPD model for viral load).

Oral MK-3682 dose absorbed via four pathways:

Pathway	%
absorbed unchanged	13.8
absorbed via pseudo-M4	31.9
absorbed via M5	9.4
absorbed via M6*	44.9

* Due to a concentration dependent elimination rate from the gut M6 compartment, part of this fraction does not reach systemic circulation. The higher the M6 gut concentration, the less M6 is actually absorbed

Above table indicates the model predicted % of MK-3682 absorbed via one of the four identified pathways. Both MK-3682 and pseudo-M4 flux into UXP, thereby contributing to efficacy whereas M5 and M6 absorption routes circumvent UXP and thereby do not contribute to efficacy.

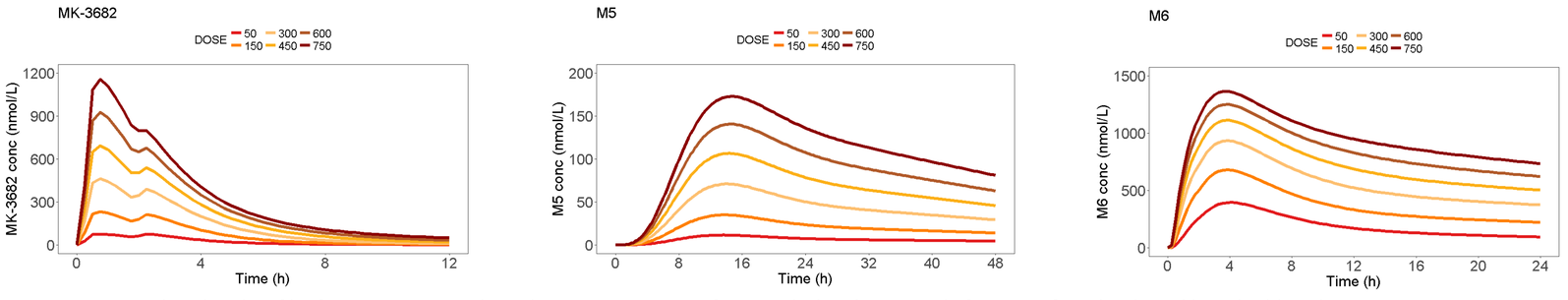

Figure 3 Typical predicted profiles for MK-3682, M5 and M6 plasma concentrations after a single dose (50-750 mg) of MK-3682 formulated as tablet in healthy volunteers

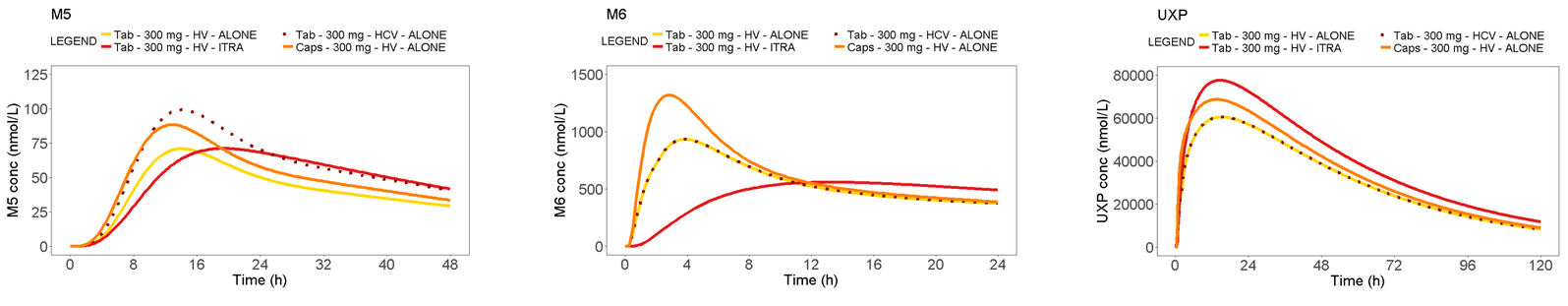

Figure 4 Typical predicted profiles for M5 and M6 plasma concentrations and projected liver UXP (active compound) concentrations after a single dose of 300 mg MK-3682, and the impact of formulation, HCV status and Itraconazole DDI on the PK

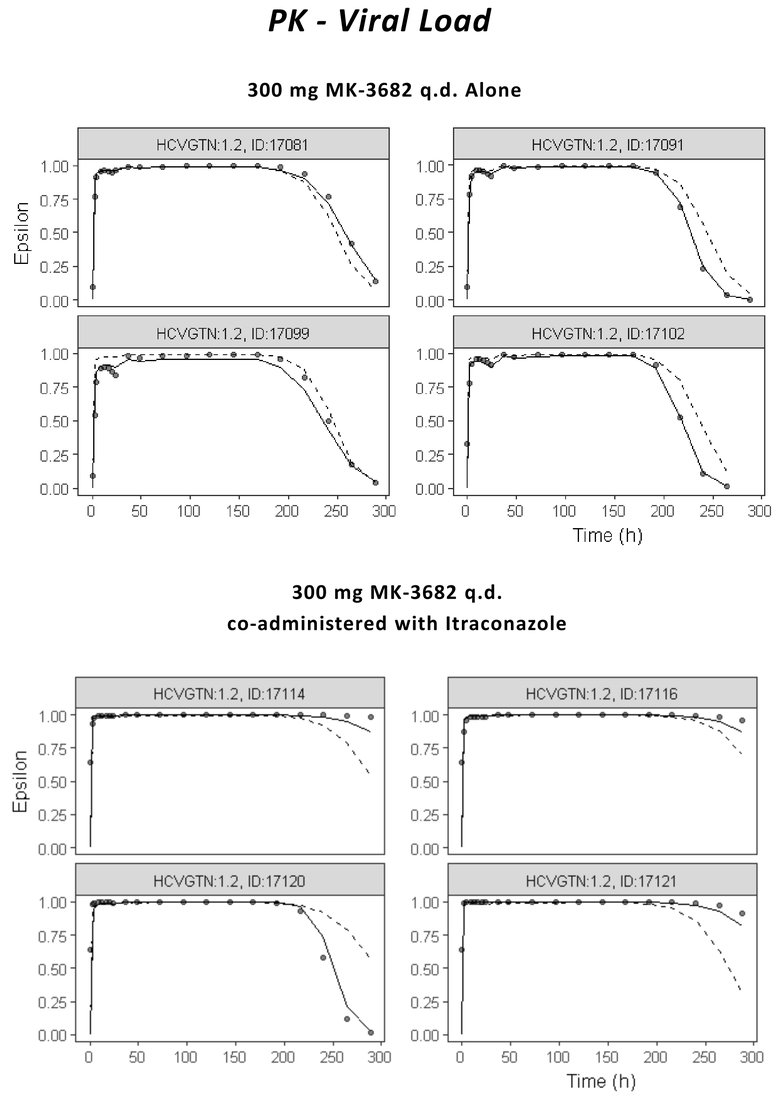

Figure 5 Individual epsilon over time curves with and without itraconazole coadministration

Conclusion

The minimal PBPK-PD model:

- **Provided a better understanding of the complex hypothesized metabolism of MK-3682**
- **Captured differences in PK between formulations and between patients and healthy volunteers**
- **Captured differences in PK in the presence of itraconazole**
- **Provided a better understanding of the relationship between plasma PK, projected liver NTP and viral load**
- **Explained the enhanced effcacy observed in patients with HCV when co-administered with itraconazole**

Overall, this framework supported and guided hypothesis generation and understanding regarding underlying metabolic pathways and perturbations under various conditions, including impact on downstream viral load.

[1] M.J.E. Brill, P.A.J. Välitalo, A.S. Darwich, B. Van Ramshorst, H.P.A. Van Dongen, A. Rostami-Hodjegan, M. Danhof, and C.A.J. Knibbe. Semiphysiologically based pharmacokinetic model for midazolam and CYP3A mediated metabolite 1-OH-midazolam in morbidly obese and weight loss surgery patients. *CPT Pharmacometrics Syst. Pharmacol.*, 5, 2016.
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