Translating PD changes from healthy volunteers to Phenylketonuria patients for MZE782 treatment using a mechanistic PK PD model

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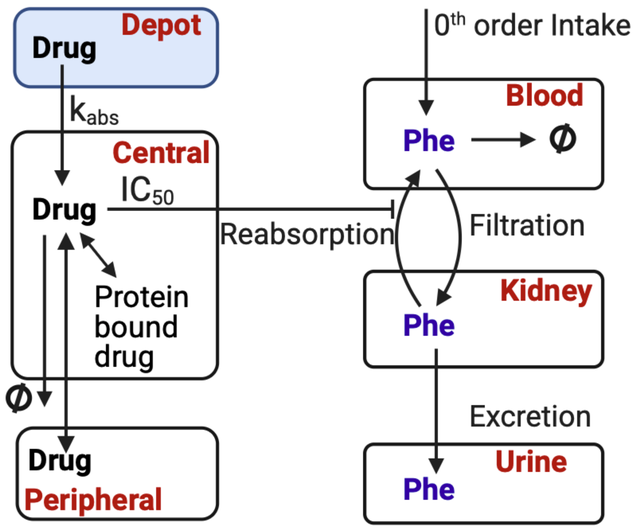
Overview

Phenylketonuria (PKU) is characterized by the toxic accumulation of phenylalanine (Phe) in blood and brain due to deficiency in Phe hydroxylase (PAH), the enzyme that breaks down Phe. Solute carrier family 6 member 19 (SLC6A19) is the major transporter responsible for free neutral amino acids uptake in the intestine and their reabsorption in the kidney. Inhibition of this transporter might be a viable therapeutic approach to safely lower the Phe levels in PKU patients. MZE782 is a small molecule inhibitor of SLC6A19, in early clinical development for treating PKU [1]. While PK and PD data from healthy volunteers (HVs) treated with MZE782 are available, this work aimed to predict Phe level changes in plasma and urine in PKU patients using a mechanistic PKPD model.

Key Takeaways

- A mechanistic PKPD model was developed to describe the drug PK and Phe homeostasis.
- The model with measured *in vitro* IC50 predicted the urine Phe excretion in HVs and PKU as well as changes in plasma Phe in PKU with repinatrabit treatment.
- Sensitivity analysis suggests increased Phe intake will not alter percent plasma Phe change relative to baseline, whereas different baseline rates of Phe metabolism may affect this endpoint.

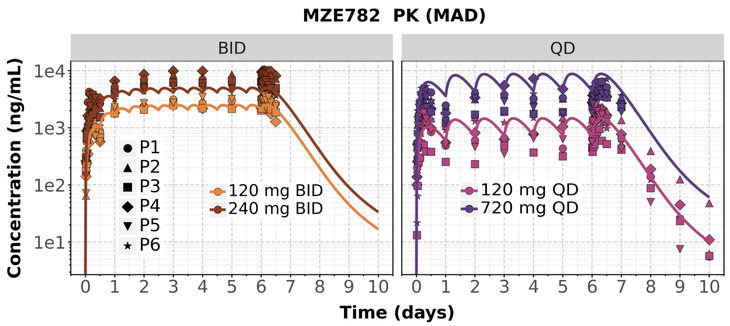
Computational Model Structure



The only differences in Phe homeostasis between HVs and PKU are Phe intake rate and metabolic rate. Clinical PK and PD data in both HVs and PKU patients treated with a molecule with the same mechanism of action, repinatrabit, were used to demonstrate the model's ability to translate PD changes from HVs to PKU (data not shown). In addition, PK and PD data from HVs treated with MZE782 were used in model development. Inhibition of the intestinal SLC6A19 and the effect of MZE782 on inhibition of Phe absorption in the gut is not currently captured in the model.

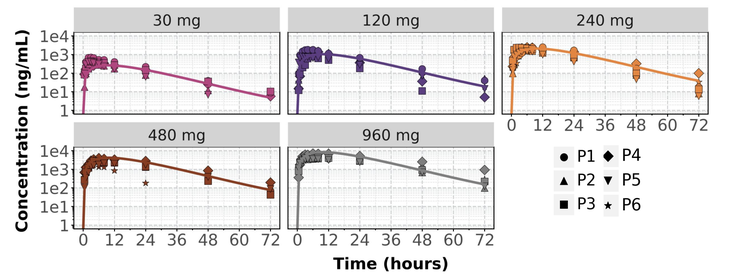
PK model calibration

The PK model was fitted to the MAD data for MZE782. Central and peripheral compartments volume, absorption half-life, distribution half-life and elimination half-life were calibrated to the available PK data [1].



PK model benchmarking

The calibrated PK model was benchmarked against MZE782 SAD PK data. Model simulations recapitulate SAD PK data.

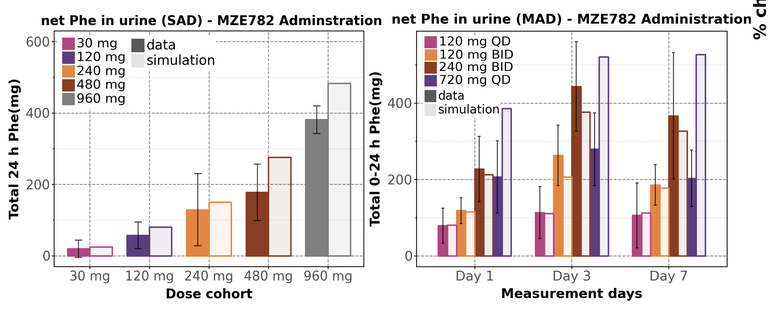


Phe homeostasis in HV and PKU

In HVs, with a daily Phe intake rate of 3 g/day, steady state Phe levels reached 65 umol/L and daily urine Phe excretion reached 5.65 mg [2]. In PKU patients, a decreased Phe intake rate of 1,628.75 mg/day and decreased metabolic rate, that is 3% of HV's metabolic rate was used. This parameterization resulted in a steady state Phe levels of 1,043.53 umol/L and daily urine Phe excretion of 90.4 mg [3].

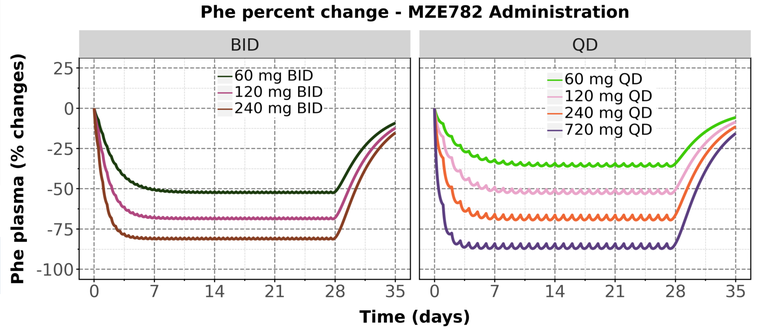
Phe excretion in HVs

Phe homeostasis model in HV and the PK model were combined to simulate excreted urine Phe amounts over 24 hours post dose for SAD and MAD studies for both repinatrabit and MZE782. Final model captured the observed urinary excretion data in HV well [1,2].



Phe in plasma and urine in PKU

The Phe homeostasis model in PKU patients and PK model were combined to simulate the change in Phe from baseline, and excreted urine Phe amounts over 24 hours interval at 28 days for both repinatrabit and MZE782 administration. The model recapitulated observed repinatrabit % change in plasma Phe data [3] and was subsequently used to simulate the model-predicted effect of MZE782 in PKU.

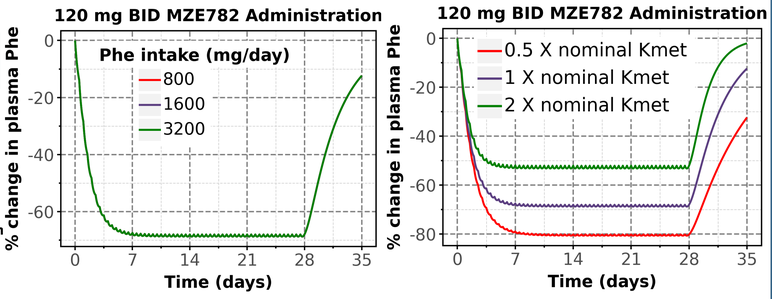


MZE782 dose (mg)	Predicted Phe in plasma (% change from baseline) Day 28	Predicted Phe in urine (mg) Day 28
Baseline	-	90.4
120 QD	-50.5	894
120 BID	-68.0	1,144
240 BID	-80.5	1,337

The predictions assume nominal metabolic rate and pre-defined baseline plasma Phe. The actual effect will differ based on intrinsic/extrinsic factors (e.g. diet, metabolism, concomitant medication) and may be higher or lower.

Sensitivity analysis

The model was used to investigate the effect of Phe metabolism rate and intake rate on % Phe change from baseline upon administering 120 mg MZE782 BID for 28 days in PKU patients. The model predicts the same level of percent change of Phe in plasma for different Phe intake rates, whereas this end point was impacted by different metabolism rates. A larger metabolic rate increased this end point compared to baseline, and a smaller metabolic rate reduced it.



Reference

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2. Wobst, H. J. et al. *SLC6A19 inhibition facilitates urinary neutral amino acid excretion and lowers plasma phenylalanine.* JCI Insight (2024) 9 (21).
3. Harding et al. *JNT-517, a first-in-class SLC6A19 inhibitor, reduces plasma phenylalanine levels in subjects with phenylketonuria in a Phase 1/2 study*. Jnana Therapeutics (2024). https://www.jnanatx.com/jnt-517-a-first-in-class-slc6a19-inhibitor/

A parsimonious mechanistic model describing Phe homeostasis and pathology for PKU is able to describe the differences in PD response between HV and PKU patients.

This approach based on mechanistic understanding provides a more robust translation from HV to PKU patients to support clinical decisions.

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