Reuse of a published model with fasting data from a novel drug formulation for a rare disorder

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Introduction

- Urea cycle disorders (UCD) are rare genetic disorders associated with hyperammonemia[1]. Sodium phenylbutyrate (BUPHENYL, AMMONAPS, NaPB) is used to treat UCD. It has a bitter taste and is labeled to be given with food[2].
- ACER-001 is an investigational product, formulated as an immediate release, taste-masked formulation of NaPB which has been shown to have a higher and more rapid exposure when administered in the fasting state.
- A food effect study, which evaluated ACER-001 (administered in the fed and fasting states) compared to BUPHENYL (administrated in the fed state), was conducted in support of a new drug application for use of ACER-001 in UCD patients.

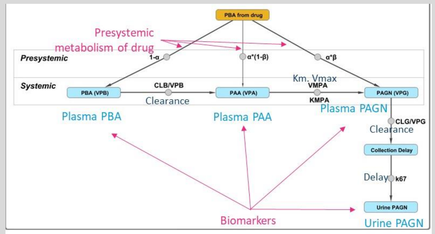
Methods

Recreate the published model in SimBiology®	The published model includes a population PK and PD model for BUPHENYL which was previously reviewed by the FDA as part of the RAVICTI NDA submission[3].
Integrate fasting PK model for ACER-001	The ACER-001 PK model was based on proprietary data.
Generate adult and pediatric VPs based on the publication	The published model includes data and parameters for different age groups. These data were used for the virtual patients (VPs).
Test to ensure model quality	Model simulations were compared to the publication and to data from the original clinical trials.
Perform model simulations to assess drug exposure	Simulations compared potential efficacy and toxicity measures for each drug across the VPs

References:
1. Brusilow, S.W. and N.E. Maestri, Adv Pediatr, 1996. 43: p. 127-70.
2. Shchelochkov, O.A., et al., Mol Genet Metab Rep, 2016. 8: p. 43-7.
3. Monteleone, J.P., et al., J Clin Pharmacol, 2013. 53(7): p. 699-710.
4. Mokhtarani, M., et al., Mol Genet Metab. 2013 Dec;110(4):446-53

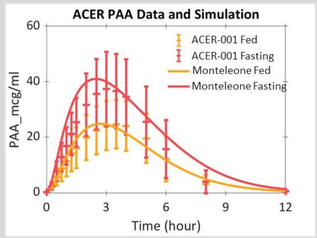
Results

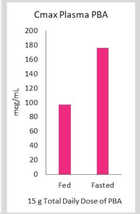
The published model was implemented in SimBiology



The equations and model parameters from the population PK model were taken from the text of the publication[3] and used to implement the model. Parameters for different age groups were used to develop Virtual Patients (VPs) as variants within the model.

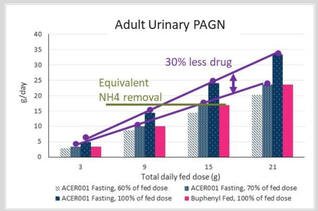
ACER-001 PK was incorporated in the model

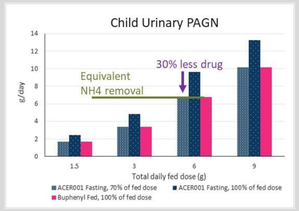


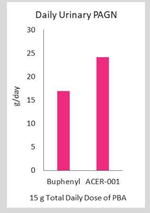


The publication used a population PK model with drug administered in the fed state[3]. Proprietary data for NaPB administered in the fasting state was used to create a fasting PK model. The fasting PK model was then incorporated into the SimBiology model.

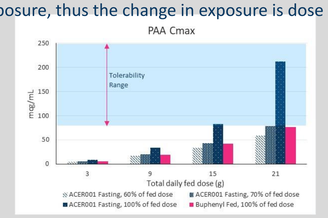
Simulations were conducted to evaluate potential drug doses



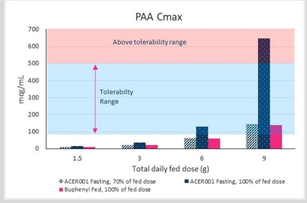




Simulations of ACER-001 (fasting) vs BUPHENYL (fed) were conducted to explore fasting dosing which would achieve equivalent urinary excretion of PAGN. BUPHENYL was dosed 3-21 g daily in adult VPs and 1.5-9 g daily in pediatric VPs. ACER-001 (fasting) was simulated at equal g NaPB dose of BUPHENYL (100% of fed dose) or at 60% or 70% of the daily fed dose of BUPHENYL. The ACER-001 fasting PK/PD model has a linear relationship between PK and drug exposure, thus the change in exposure is dose linear.



Simulations in adult VPs were conducted to span a full range of NaPB drug doses. The tolerability range was set based on published data[4].

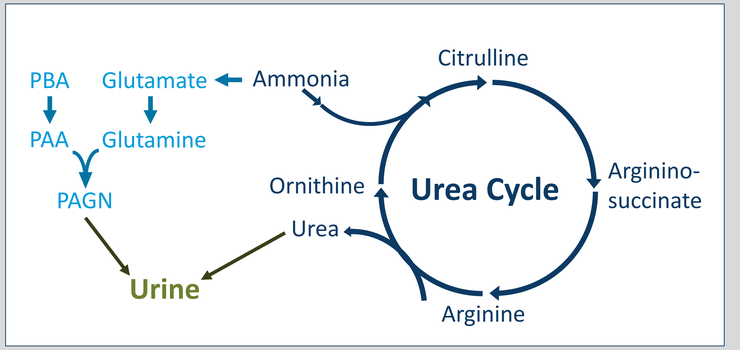


Simulations in pediatric VPs were conducted to span a full range of NaPB drug doses based on the weight of a 3-5 year old child. The tolerability range was set based on published data[4].

Discussion

Drug development for rare disorders is complex. With few subjects available, designing trials and recruiting enough subjects to reach a meaningful outcome can be difficult. Modeling can help support drug development for rare disorders by optimizing trial design and dosing.

Because the data are limited for UCD, modeling provided a method to evaluate the impact of potentially dosing without food on the efficacy and potential toxicity using data from a new investigational formulation of NaPB.



In UCD, a mutation in a urea cycle enzyme results in lower activity and excretion of ammonia into the urine as urea is limited. PBA provides an alternative pathway for the removal of ammonia from the body. PBA: phenylbutyrate, PAA: phenylacetic acid, PAGN: phenylacetylglutamine.

Consistent with clinical observations, fasting administration of ACER-001 or Buphenyl (Ammonaps) resulted in increased drug exposure in the Virtual Patients.

Based on the revised model, fasting administration of ACER-001 or Buphenyl (Ammonaps) in the Virtual Patients is predicted to increase efficacy in proportion to the increased drug exposure, suggesting a 30% decrease in the administered dose under fasting conditions would still achieve the same level of exposure (efficacy and tolerability) as dosing under fed conditions.

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