Using Modeling to Assess the Impact of Food on the PD of a Novel Drug for Urea Cycle Disorders

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Background

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.

Urea cycle disorders (UCD) are rare genetic disorders associated with hyperammonemia¹. In UCD, a mutation in a urea cycle enzyme results in lower activity and excretion of ammonia into the urine as urea is limited.

Sodium phenylbutyrate (Buphenyl, Ammonaps, NaPBA) is used to treat UCD. It has a bitter taste and is labeled to be given with food². Phenylbutyrate (PBA) the active moiety provides an alternative pathway to assist in the removal of ammonia from the body.

ACER-001 is an investigational product, formulated as an immediate release, taste-masked formulation of NaPBA which has been shown to have a higher and more rapid exposure when administered in the fasting state as compared to the fed state.

A simulated food effect study, which evaluated ACER-001 (administered in the fed and fasting states) compared to Buphenyl (administered in the fed state), was conducted in support of a new drug application for use of ACER-001 in UCD patients.

Because the number of UCD patients that can be enrolled in clinical trials is limited, computer modeling provided a method to evaluate the impact of potentially dosing without food on PK exposure as a surrogate for efficacy and potential toxicity using data from a new investigational formulation of NaPBA.

Methods

A previously published population pharmacokinetic/pharmacodynamic (PKPD) model for UCD was modified for this work³.

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 submission³.

Integrate fasting PK model for ACER-001

The ACER-001 PK model was based on proprietary PK data in healthy volunteers.

Generate adult and pediatric VPs based on the publication

The published model includes data, initial conditions, and parameters for different age groups. The parameters and initial conditions for each group defined a virtual patient (VPs) for that age group.

Test to ensure model quality

The model simulations were compared to the original Monteleone publication and to data from the original clinical trials used for the population PK model. (Results 1)

Perform model simulations to assess drug exposure

The simulations compared PK exposure and PD measures for each across the VPs. (Results 2-5)

Results

In the model, ACER-001 when administered in the fasting state (Fasting PK) showed reasonable agreement between observed and simulated results. Buphenyl simulation results were compared to data from Monteleone 2013.

Results 1. To validate the model, simulation of a single dose of 5 g NaPBA using the fasting PK or the fed PK was compared to data from Monteleone 2013 and ACER-001 proprietary data. Simulation results above are shown as a line and data are shown as circles with standard deviation bars.

Results 2. PK model simulations show that ACER-001 administered with a fasting PK increased the peak PBA concentration (Cmax) in both Adult and Child Virtual Patients. ACER-001 (Fasting PK) simulations are compared to Buphenyl (Fed PK). The increase in drug concentration in the simulations was dose proportional due to increased absorption of drug in the model.

Results 3. The maximum concentration of PAA was increased when ACER-001 was simulated with fasting PK compared to Buphenyl with fed PK. Simulations showed the PAA Cmax increased in the Child Virtual Patient (right) which has limited enzyme capacity of glutamine N-acetyltransferase and thus had limitations on metabolizing PAA to PAGN (note y-axis scales). PAA plasma concentrations ≥ 500 μg/dL have been reported to be associated with reversible neurological adverse events4. In the simulations shown, the maximum concentration of PAA did not exceed 500 μg/dL.

The previously published population PKPD model was developed using data from the Buphenyl administered in the fed state3. Proprietary data for ACER-001 administered in the fasting state was used to create a fasting PK model. The fasting PK model was then incorporated into the SimBiology model.
Results

Results 4. Dose response simulations of ACER-001 (Fasting PK) vs. Buphenyl (Fed PK) were conducted to evaluate the simulated amount of blood PAGN as a surrogate of efficacy. Simulation administration of ACER-001 (Fasting PK) had a higher PAGN Cmax than Buphenyl (Fed PK).

Results 5. Simulated Daily Urinary excretion of PAGN was evaluated in the Virtual Patients. Dose response simulations of ACER-001 (Fasting PK) vs. Buphenyl (Fed PK) had a higher excretion of PAGN in the Virtual Patients given ACER-001. Simulations had a 30% higher excretion of PAGN in the Virtual Patients modeled with ACER-001 with fasting PK as compared to Buphenyl with fed PK.

Conclusions

❖ Consistent with clinical observations, administration of ACER-001 with fasting PK resulted in increased drug exposure in the Virtual Patients as compared to Buphenyl (Ammonaps) with fed PK.

❖ Based on the revised PK/PD model, administration of ACER-001 with a fasting PK in the Virtual Patients showed increased efficacy based on the increased PBA exposure. Suggesting a 30% decrease in the administered dose under fasting conditions (premeal) would achieve the same level of exposure (efficacy and tolerability) as dosing under fed conditions.

❖ The model and results presented here are intended as a hypothesis generating work and further analysis should be conducted.

References: