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Physiologically-Based Pharmacokinetic (PBPK) Modeling of Oral Absorption of 5-flucytosine to Support Development of a Sustained-Release Formulation for Treatment of Cryptococcal Meningoencephalitis

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PURPOSE

5-Flucytosine (**5FC)** is used for the treatment of **cryptococcal meningoencephalitis (CM)**. Due to its short plasma half-life and safety profile, it is currently dosed four times a day. This frequent dosing involves a high risk of low adherence, with potential consequences for both pharmacodynamic effect and toxicity [1,2]. To address this problem, and the challenge of administration in severely ill *non per os* patients, a **sustained-release (SR)** pellet formulation is currently being developed to decrease dosing frequency and to allow naso-gastric tube administration, thus improving the treatment. A **model-informed drug development (MIDD)** strategy was implemented to inform decisions during the project [3].

In a first step, using a PBPK model, three SR prototype formulations:

- Formulation-B - releasing not more than 20% flucytosine *in vitro* in 1 hour
- Formulation-C - releasing not more than 35% flucytosine *in vitro* in 1 hour
- Formulation-D - releasing not more than 45% flucytosine *in vitro* in 1 hour

were developed for safety and **plasma pharmacokinetics (PK)** evaluation in fasted healthy participants (study 1), along with a commercial **immediate-release (IR)** tablet.

To further support dosing and guide formulation selection in a subsequent clinical study (study 2: fed study in healthy participants), the legacy PBPK model was updated with the PK data obtained in study 1.

OBJECTIVE

The aim of this analysis was to predict the food effect for the SR and IR formulations in healthy participants, and to suggest a dosing regimen for the study in fed healthy participants.

METHODS

PBPK modeling was performed in PK-Sim v.9.1. A legacy PBPK model for 5-FC had previously been developed based on literature data for an IR formulation [4]. The PK data obtained from study 1 was used to further update and refine the legacy model.

The final model included a fraction unbound in plasma set to 97% [5] and elimination attributed to glomerular filtration [6]. The intestinal permeability was estimated at a high value to describe the fast T_{max} seen for 5FC in aqueous solution [6] and Weibull functions were estimated for the IR and SR formulations to describe the slower absorption for undissolved formulations. In addition, colonic absorption was decreased to describe the observed PK data.

The model was evaluated by visual inspection of the concentration-time profile and comparison of simulated vs. observed PK parameters. To predict the food effect on PK for 5-FC, gastric emptying time was prolonged in accordance with the available implementation in PK-Sim. The solubility of 5-FC was not considered to be altered by food intake, as it is a drug with high water solubility, and thus not expected to be affected by solubilization by bile salts.

A therapeutic interval of C_{max} not higher than 100 mg/L and C_{trough} between 20-70 mg/L was considered in this analysis.

RESULTS

The refined 5-FC PBPK model described the PK data in study 1 well (Figure 1), with absolute average fold error (AAFE) values for AUC_{last} and C_{max} of 1.13 for both parameters.

Of the three SR formulations, the fastest release formulation (formulation D) had the highest bioavailability (62%) relative to the IR tablet in study 1. Prolonged GET enables a longer time for absorption and the predicted relative bioavailability for formulation D in fed state increased to 80%, still with the highest bioavailability of the three SR formulations.

The estimated doses required for treatment D to be within the therapeutic target concentrations with a bi-daily dosing were approximately 6000 mg in fasted state and 5000 mg in fed state (Figure 2).

According to simulations, a dose of 6000 mg can be given as a first dose regardless of prandial state (if unknown for unconscious patients when admitted to the hospital) without exceeding the therapeutic C_{max} concentration (Figure 3).

In addition, the simulations do not support a loading dose being given together with the SR formulation to achieve comparable PK as the IR formulation, since the simulated difference in time to reach same C_{max} as IR was only about 20 min (Figure 3).

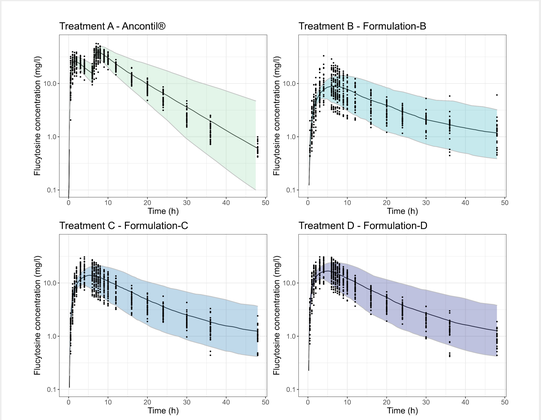

Figure 1. *Simulation with final model in fasted state compared to observed data from study 1 on a log-linear scale. Black dots represent the observed data, black line and shaded area represent the median and 5-95% range for the simulation. Treatment A dosing was 1500 mg at t=0 and t=6 and Treatment B-D dosing was 3000 mg at t=0. BLQ values are not displayed.*

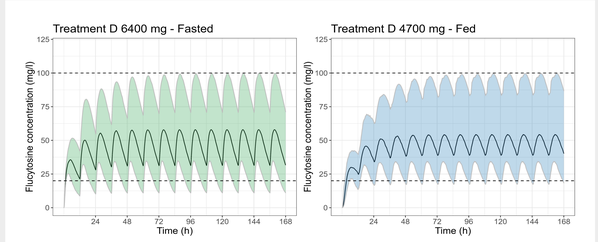

Figure 2. *Predicted concentration-time profiles of 5-FC for optimized dosing b.i.d. of Treatment D in fasted and fed state. Solid lines represent the predicted median and the shaded areas represent the 90% prediction interval. Dashed lines represent the limits of the therapeutic interval of 5-FC (20-100 mg/L).*

Table 1. *Predicted parameters for the IR and SR of 5-FC in fasted state and predicted parameters for the SR in fed state. Values are presented as median ± SD.*

Parameter (unit)	IR - Fasted (Study 1)	SR - Fasted (Study 1)	SR - Fed (Study 2)
AUC_{inf} (mg*h/L)	524±320	327±240	417±260
C_{max} (mg/L)	39.2±6.8 (second dose)	16.9±3.8	19.9±4.2
T_{max} (h)	7.4±0.3 (second dose)	4.7±1.3	7.2±2.1
Relative bioavailability (%)	-	62	80

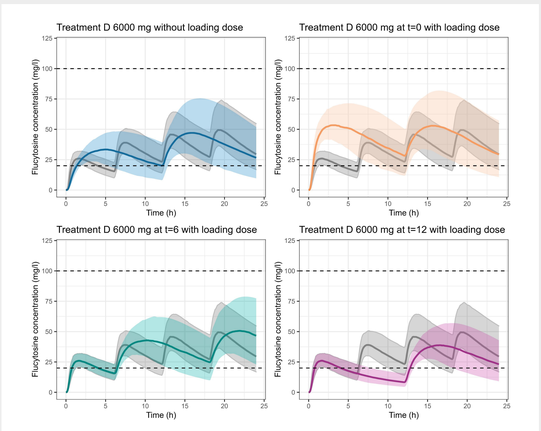

Figure 3. *Predicted concentration-time profiles of 5-FC in fasted state after IR administration 4-times a day (grey-shaded area) and after SR administration (treatment D here) given twice a day at 6000 mg with different start times (0, 6h and 12h) with/without loading dose (color-shaded area). Solid lines represent the predicted median and the shaded areas represent the 90% prediction interval. Dashed lines represent the limits of the therapeutic interval of 5-FC (20-100 mg/L).*

CONCLUSIONS

1. The estimated doses for 5-FC plasma concentrations to be within the therapeutic target with bi-daily dosing were approximately 5000 mg in fed state and 6000 mg in fasted state.
2. A loading dose of the SR formulation was not needed for it to be comparable to the IR formulation, according to the model.
3. The risk of exceeding the therapeutic safe range, due to uncertainties in prandial state, was predicted to be low, even at a higher starting dose (6000 mg).
4. The model will be refined based on data from study 2 and used in the subsequent step of the MIDD strategy, informing the design of a clinical Phase II study in CM patients.

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