MODEL-BASED APPROACH OF DOSE SELECTION AND OPTIMAL PK SAMPLING OF FOSTEMSAVIR FOR PEDIATRIC PATIENTS WITH MULTIDRUG RESISTANT HIV-1 INFECTION

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Introduction

- Fostemsavir (FTR) is a human immunodeficiency virus type 1 (HIV-1) attachment inhibitor in Phase 3 development for the treatment of heavily treatment-experienced (HTE) adults and children with multidrug-resistant HIV-1 infection.
- FTR is an extended-release prodrug and is hydrolyzed by alkaline phosphatase in the gastrointestinal lumen to its active moiety, temsavir (TMR). TMR is primarily metabolized by esterase-mediated hydrolysis with contributions from cytochrome P450 (CYP) 3A4.
- The current analysis demonstrates the application of a model-based approach to select optimal doses and a PK sampling strategy to help design an efficient clinical trial of FTR in pediatric patients by leveraging the comprehensive data from the adult program.

Objectives

- To identify the optimal dosing regimen(s) by body weight for FTR in pediatric patients with multidrug-resistant HIV-1 infection.
- To identify the optimal PK sampling times and the number of subjects for which intense sampling is to be collected.

Methods

- The TMR adult population (POP) PK model[1] with weight-based allometric scaling was used for simulations with parameter uncertainty using the mrgsolve package in R. 500 trials were simulated using different doses by weight bands, and scenarios accounting for both the presence and absence of CYP3A4 inducer or inhibitor to evaluate the probability of success (PoS) based on Cmax and Ctau-defined criteria to maintain exposures comparable to those observed in the adult population.[2]
- Clinical trial simulations were also conducted to assess optimal PK sampling schemes and subject numbers. The final TMR POP PK model was used for parameter estimation and compared to the true value for each subject to calculate the precision of PK parameter estimates.

Results

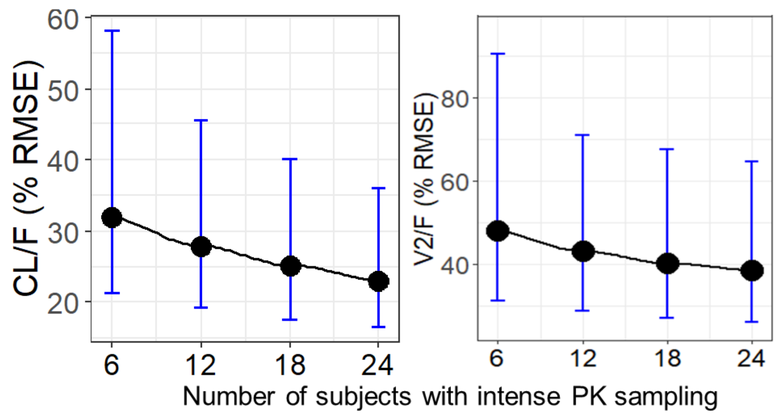
- Dosing simulations demonstrated that the adult dose of FTR 600 mg BID for pediatric subjects ≥35 kg and FTR 400 mg BID for subjects ≥20 to <35 kg meet defined criteria by providing comparable adult TMR exposure that established FTR safety and efficacy (Table 1).
- Figure 1 summarizes the CL/F and V2/F precision as measured by % root mean square error (% RMSE) across different sampling schemes and number of subjects with intense sampling.
- This analysis identified that for the intense sampling portion of the study, 6 PK sampling times in a dosing interval (1, 2, 4, 6, 8, and 12 h post-dose) ±30 min in at least 12 of 50 subjects in the ≥35-kg cohort would give the optimal precision in CL/F and V2/F (Figure 1).

Table 1. Percent Probability of Maintaining Cmax and Ctau Threshold Levels By Pediatric Weight Bands

	Scenario	Criteria[a]	Weight bands (kg)							
			20 - ≤25	25 - ≤30	30 - <35	35 - ≤40	40 - ≤45	45 - ≤50	50 - ≤55	40 - ≤70
Proposed Dose Regimen			**400 mg BID**			**600 mg BID**				
Cmax PoS[b] (%)	FTR Alone	10 msec, 80%	99.8	100				100		
	FTR + Inhibitor	10 msec, 80%	62.6	94.4	99.8	69.0	96.0	99.6	99.8	100
Ctau PoS[b] (%)	FTR Alone[c]	134 ng/mL, 80%	97.2	96.4	94.2			100		99.8
	FTR + Inducer[d]	49 ng/mL, 80%	90.2	84.0	85.6	99.6	99.4	98.4	98.6	98.0

[a]Criteria represented as target [e.g., 10 msec QTc threshold for Cmax (corresponding to 7500 ng/mL) or 10th percentile of Ctau] and percentage participants aimed to achieve success in (e.g., 80% is success in 8 out of 10 participants). [b]Summary of probability of success (PoS) based on 500 trials containing 100 participants in each weight band across different scenarios in each trial. [c]Based on Phase 3 data for FTR 600 mg BID alone, adult 10th percentile Ctau = 134 ng/mL. [d]Based on Phase 3 data for FTR 600 mg BID with a moderate inducer, adult 10th percentile Ctau = 49 ng/mL.

Figure 1. % RMSE of CL/F and V2/F Across Different Numbers of Subjects With Intense Sampling



The solid black circles represent the median % RMSEs, and the lower and upper whiskers represent the 5th and 95th percentiles % RMSEs of CL/F and V2/F with no PK parameters fixed or with Q, V3/F, D1, and KA fixed.

Discussion

- The doses were selected to maintain a balance in safety and efficacy while retaining a simplified dosing regimen in subjects with HIV-1 weighing down to 20 kg.
- Optimal PK sampling analysis helped to identify the PK sampling scheme and demonstrated that intense PK sampling data from 12 subjects in the ≥35-kg cohort would provide adequate confidence in selecting doses that provide target Cmax and Ctau values.

Conclusions

- The model-based approach allowed selecting optimal doses for pediatric subjects with body weight down to 20 kg.
- Based on the analysis, optimal PK sampling times for intensive sampling are 1, 2, 4, 6, 8, and 12 h post-dose with intensive PK sampling to be conducted in at least 12 subjects in the ≥35-kg cohort.

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References: 1. Parasrampuria et al. CROI 2020; Boston, MA. Poster 463. **2.** Lagishetty et al. *Clin Transl Sci*. 2020 [Epub ahead of print].

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