FOSTEMSAVIR EXPOSURE-RESPONSE RELATIONSHIPS IN TREATMENT EXPERIENCED HIV PATIENTS

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Introduction

- Fostemsavir (FTR) is an oral prodrug of its active moiety, temsavir (TMR), an investigational HIV-1 attachment inhibitor
- Phase 3 efficacy exposure-response (ER) relationships in Randomized Cohort of the heavily treatment-experienced (HTE; multi-drug resistant) HIV-1 patients dosed with FTR 600 mg BID, and safety ER relationships from Phase 2b (generally treatment experienced (GTE), dosed with FTR 400, 800 mg BID and 600, 1200 mg QD) and Phase-3 (HTE patients in both Randomized and Non-Randomized Cohorts, dosed with FTR 600 mg BID) were evaluated

Methods

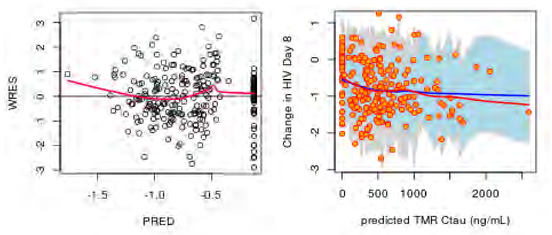
- Individual PK parameters estimated from a population PK model were combined with efficacy and safety endpoints to evaluate ER relationships
  - Plasma TMR exposure metrics included in efficacy ER analyses were observed trough concentration (Ctau), model predicted Ctau, average TMR concentration (Cavg), trough concentration corrected for phenotypic sensitivity (Ctau/protein binding adjusted IC50, (PBIC50), Ctau/ protein binding adjusted IC90, (PBIC90))
- Efficacy endpoints explored included:
  - In Randomized Cohort only, change in plasma HIV-1 RNA from Day 1 to 8 (functional monotherapy) and change in plasma HIV-1 RNA from Day 1 to Week 24, proportion of subjects with >0.5 and >1.0 $\log_{10}$ decrease in HIV-1 RNA on Day 8, proportion of subjects with HIV-1 RNA <40, <200 and <400 copies/mL at Week 24
  - In addition, covariates of virologic (TMR IC50, baseline viral load and gp160 substitutions), immunologic (CD4+ T-cell count, CD8 T-cell count), and demographic factors (age, weight, gender, race, region) as predictors of virologic response were investigated
  - Simulations were conducted to predict virologic responses on Day 8 with food, co-medications (moderate CYP3A inducers, strong CYP3A inhibitor) and varying body weight. 500 trials were simulated where each trial included 364 subjects. For change in plasma HIV-1 RNA, the median and 95% CI for each trial was calculated, then the median 2.5th, 50th and 97.5th values of the 500 simulations were calculated. For proportion of subjects achieving > 0.5 $\log_{10}$ reduction in HIV-1 RNA, the median and 95% CI of the 500 simulated results were calculated
- Safety endpoints explored included:
  - Change from baseline in AST, ALT, CPK, SCr, QTcF and occurrence of rash up to Week 24
- Following graphical exploration, linear, inhibitory Emax and logistic regression models for different endpoints were explored

Results

Change in Plasma HIV-1 RNA from Day 1 to Day 8

- 258 subjects (193 on FTR 600 mg BID and 65 on placebo) were included in the ER analyses for Day 8 efficacy endpoint
  - Out of 272 subjects in the Randomized Cohort of the Phase 3 study, a total of 258 subjects had plasma HIV-1 RNA data on both Day 1 and Day 8 and PK data
- Shallow and highly variable Emax ER relationship was observed between post-hoc plasma TMR Ctau and change in plasma HIV-1 from Day 1 to Day 8
  - Emax (maximum effect) parameter was 1.00 $\log_{10}$ c/mL (17.1%, relative standard error (RSE)), E0 (change in plasma HIV-1 RNA from Day 1 to Day 8 for placebo) was -0.129 ($\log_{10}$ c/mL) and EC50 (plasma TMR Ctau which results in 50% of maximum effect) was 64.3 (ng/mL) with poor precision (RSE >66%) and with high residual variability (approximately 65% of Emax)
- Baseline plasma HIV-1 RNA and baseline CD4+ were significant covariates, higher baseline values, greater Day 8 virologic response
  - For every 10,000 unit increase in baseline plasma HIV-1 RNA concentration over (the median) 44,940 c/mL, virologic response increases by approximately 3% for baseline CD4+ count >20 cells/mm^3 and 2.34% for baseline CD4+ count <20 cells/mm^3
  - At baseline plasma HIV-1 RNA of 44,940 c/mL, Day 8 virologic response is 45.3% higher for subjects with baseline CD4+ count >20 cells/mm^3 compared with subjects with baseline CD4+ count <20 cells/mm^3.
  - Age, gender, race, body weight, geographic region and the following baseline factors: IC50, IC50 fold change and number of predefined genotypic substitutions of interest within the GP160 domain, and CD8+ count had no significant effect on Day 8 virologic response
  - Model goodness of fit plots are shown in Figure 1

Figure 1. Goodness of Fit and Visual Predictive Check (VPC) Plots for Relationship Between Change in Plasma HIV-1 RNA from Day 1 to Day 8 and Post-hoc Plasma TMR Ctau

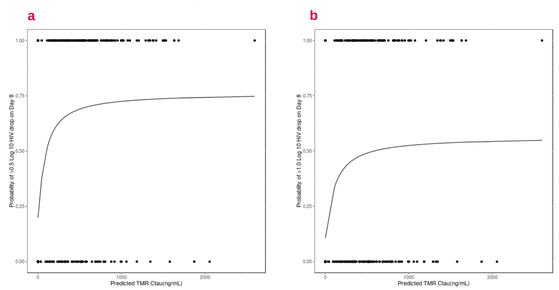


Blue line is simulated median and red line is observed median. Blue shaded area represents 90% prediction interval. Points represent observed data.

Proportion of Subjects Achieving >0.5 $\log_{10}$ and >1 $\log_{10}$ Reduction in Plasma HIV-1 RNA on Day 8

- Logistic regression Emax model was utilized to characterize relationship between plasma TMR Ctau and proportion of subjects achieving >0.5 $\log_{10}$ and > 1 $\log_{10}$ decrease in plasma HIV-1 RNA on Day 8
  - Baseline HIV-1 RNA and baseline CD4+ count were significant covariates
  - Model predicted probability of >0.5 $\log_{10}$ and >1.0 $\log_{10}$ decrease in plasma HIV-1 RNA on Day 8 is presented in Figure 2a and Figure 2b, respectively

Figure 2 Logistic regression model predictions for probability of >0.5 $\log_{10}$ and >1.0 $\log_{10}$ decrease in plasma HIV-1 RNA on Day 8



Efficacy ER simulation results

- Simulations show that decreased plasma TMR exposure observed with moderate CYP3A inducers and increased plasma TMR exposure observed with strong CYP3A inhibitors do not result in clinically relevant changes in Day 8 virologic response for FTR 600 mg BID (Table 1)
- Administration of FTR 600 mg with a standard meal resulted in median 68% higher plasma TMR Ctau, a median 0.057 $\log_{10}$ c/mL higher Day 8 virologic response and approximately 4% more subjects with > 0.5 $\log_{10}$ reduction in Day 8 plasma HIV RNA compared with administration under fasted state (Table 1)
- Based on simulations, there was almost no difference in virologic response between subjects at extremely low (40 kg) and extremely high (150 kg) body weights (Table1)

Week 24 Efficacy E-R Model Results

- 235 patients were included in the ER analyses for Week 24 efficacy endpoints (change in plasma HIV-1 RNA from Day 1 to Week 24, proportion of subjects with HIV-1 RNA <40c/mL, <200c/mL and <400 c/mL). No clinically relevant relationship between post-hoc plasma TMR Ctau and Week 24 efficacy endpoints could be established

Table 1. TMR Exposure Efficacy Response Simulation Results

Scenario FTR 600 mg BID	Change in plasma HIV-1 RNA from Day 1 to Day 8, Median (95% CI)	Proportion of Subjects >0.5 $\log_{10}$ c/mL on Day 8, Median (95% CI)
No inducer/inhibitor	-0.782 (-2.20, 0.600)	0.626 (0.581, 0.670)
Mild/moderate CYP3A inducer alone	-0.685 (-2.11, 0.692)	0.547 (0.503, 0.591)
CYP3A inhibitor alone	-0.834 (-2.25, 0.535)	0.673 (0.625, 0.717)
Standard meal	-0.782 (-2.20, 0.600)	0.626 (0.581, 0.670)
Fasted	-0.725 (-2.14, 0.647)	0.58 (0.533, 0.62)
40 kg body weight	-0.807 (-2.22, 0.565)	0.648 (0.602, 0.69)
150 kg body weight	-0.745 (-2.15, 0.627)	0.593 (0.547, 0.635)

Safety ER results

- 559 subjects were included in the safety ER analyses for clinical lab data through Week 24, and 553 subjects were included in the ER analysis for ECG from Phase 2b and Phase 3 studies
- No exposure-safety relationships were evident between posthoc plasma TMR exposure metrics (steady state Cavg or Cmax) and safety endpoints of interest in graphical analysis

Conclusions

- Shallow and highly variable ER relationship was observed with posthoc plasma TMR Ctau and change in plasma HIV-1 RNA from Day 1 to Day 8 during FTR functional monotherapy
  - Baseline plasma HIV-1 RNA and CD4+ were a significant covariate
- Simulations showed PK changes associated with effects of moderate CYP3A inducers, strong CYP3A inhibitors, prandial status, and extremes of body weight do not result in clinically relevant changes in Day 8 virologic response for FTR 600 mg BID and no FTR dose adjustment is needed for these factors
- No ER relationship was evident between plasma TMR Cmax/Cavg/Ctau and efficacy or safety endpoints at Week 24

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