Efavirenz (EFV) 400 versus 600 mg daily: Results of the ENCORE1 Intensive PK Sub-Study

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INTRODUCTION

• Efavirenz (EFV)-based combination therapy dosed 400 mg once daily is recommended as first-line treatment of HIV-infected treatment-naïve patients.1
• ENCORE1, an ongoing study in treatment-naïve HIV-infected adults assessing reduced dose EFV, recently showed virological non-inferiority of 400 mg EFV once daily compared to the standard dose of 600 mg at 48 weeks of therapy.2
• Efficacious dose reduction may provide added clinical benefit by reducing dose-related toxicities as well as decreasing treatment costs.

OBJECTIVES

• Determine and compare the pharmacokinetics (PK) of EFV dosed at 400 mg and 600 mg once daily in a sub-group of patients enrolled in ENCORE1.
• Evaluate the influence of patient demographics and CYP2B6 516G>T and 983T>C host genetics on EFV exposure.

METHODS

• Patients & PK Sampling: Consenting, HIV-infected, treatment-naïve adults were enrolled in the intensive PK sub-study of ENCORE1. Patients were randomised to receive 400 mg or 600 mg EFV once daily in combination with Truvada® (tenofovir disoproxil fumarate/emtricitabine, 300/200 mg once daily).
• Intensive PK sampling was undertaken at steady-state between 48–8 weeks of therapy, pre-dose (0 h), 2, 4, 8, 12, 16 and 24 h post-dose.
• EFV plasma concentrations were quantified by a fully validated LC-MS/MS method with a lower and upper limit of quantification of 0.025 and 10 mg/L, respectively.3

• Genotyping: Total genomic DNA was extracted from whole blood and samples quantified and normalised to 20 ng/µL.
• Genotyping for CYP2B6 516G>T (rs3745274) and CYP2B6 983T>C (rs2839949) was performed using TaqMan assays and identified by real time PCR-based allelic discrimination.

• Data Analysis: EFV PK parameters (apparent oral clearance, CL/F; area under the concentration-time curve over 24h, AUC24; maximum concentration, Cmax; representation of mid-dose interval, C12; trough concentration 24 post-dose, C24) were calculated by non-compartmental methods using WinNonlin™.

• To assess differences between doses and genotypes, geometric mean ratios (GMR) and 90% CI were calculated using log-transformed data then expressed as linear values. The primary endpoint was GMR EFV AUC24 for comparison of randomised doses. Changes were considered significant if the CI did not cross 1 (primary analysis).
• A log transformation did not correct for non-normality in PK parameters when comparing doses and genotypes a post-hoc, non-parametric analysis was performed (Mann-Whitney U test, p<0.05 considered significant).
• Multivariate linear regression was carried out to evaluate the influence of patient weight, age, sex, CYP2B6 516G>T and EFV dose on EFV log AUC24 and log C24.

RESULTS

• Patients: 46 patients (400 mg n=28, 600 mg n=18) participated in the PK sub-study at sites in South Africa, Thailand, UK and Argentina (n=15 female; 37% African, 22% Asian, 41% Caucasian). Mean (s.d.) age, weight and baseline CD4 count were 36 years (10), 71 kg (16) and 269 (95) cell/mm3, respectively.
• PK: EFV concentrations over the 24h dosing interval and PK parameters stratified by dose are presented (Figure 1, Table 1).
• EFV AUC24, Cmax and C24 were significantly lower in the 400 mg dosing group (Table 1). C12 and C24 were below the suggested MEC (1.0 mg/L) in 25 and 46% and 6 and 28% of patients receiving 400 mg and 600 mg EFV, respectively.
• Genotyping: Genotype data were available for 44/46 patients. Genotype frequencies were 52, 35 and 9% for CYP2B6 516G>G, GT and TT, respectively.

• Stratified for dose, significant differences remained for 400 mg EFV but only C24 was significantly lower for GG (n=6) vs G/T+T (n=8) for 600 mg EFV (Figure 2). CYP2B6 983T>C was not assessed given that 43/44 were wild-type (TT).
• Multivariate analysis revealed CYP2B6 516G>T, EFV dose and weight were independently associated with log AUC24 (r2=0.44, log AUC24=1.79+0.16*dose)+(0.22*G/T-0.04*weight); p=0.0001 and CYP2B6 516G>T and dose with log C24 (r2=0.35, log C24=1.13*(G/T-0.15)*dose); p=0.0001.
• Overall 78% of patients achieved viral load <50 copies/mL at 48 weeks (missing viral load tests were classified as detectable).
• Due to small sample size, a formal PK-pharmacodynamic (PD) analysis was not possible. At week 48, 5/28 (18%) had detectable viral loads (≥50 copies/mL) for 400 mg EFV, 2 of which were <1.0 log10 (MEC) for C12 and C24. For 600 mg EFV, 5/18 (28%) had viral loads ≥50 copies/mL, 1 was below the MEC at 24 weeks.

CONCLUSIONS

• Patients receiving 400 mg EFV had comparable viral suppression to 600 mg once daily (consistent with main ENCORE1 findings) despite significantly lower EFV exposure and higher proportions of C12 and C24 below the suggested MEC at PK sampling.
• These data challenge the currently defined PK targets for therapeutic success.
• CYP2B6 516G>T genotype and weight were independently associated with EFV PK (AUC24, C24), which is consistent with previous reports.
• PK-PD modelling of the data obtained in ENCORE1 is currently ongoing to elucidate predictors of EFV PK and response in a heterogeneous HIV-infected patient population naïve to antiretroviral therapy.