Pharmacokinetics and pharmacodynamics of etravirine in treatment-experienced HIV-1-infected patients: pooled 48-week results of DUET-1 and DUET-2

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**Abstract**

**Background**
Etravirine (ETR; TRC125) is a next-generation NNRTI with potent activity against both wild-type and NNRTI-resistant HIV. DUET-1 and DUET-2 are identical designed, ongoing, Phase III, double-blind, randomized trials of ETR versus placebo, both with an investigator-selected background regimen (BR) including ritonavir-boosted darunavir (DRV/r). The relationship between ETR pharmacokinetics and pharmacodynamics over 48 weeks from these trials was investigated.

**Methods**
Population pharmacokinetics for area under the plasma concentration-time curve (AUC) and predose plasma concentration (C0) were estimated using Bayesian feedback. Analysis of covariance (ANCOVA) and logistic regression with generalized additive modeling (GAM) were used to analyze pharmacokinetics/pharmacodynamic (PK/PD) relationships with efficacy endpoints and safety.

**Results**
Of the 1,203 patients enrolled, 599 were randomized to ETR, and PK data from 575 were available. Mean (standard deviation) (SD) ETR AUC0–24h and C0 were 5,506 (4,710) ng·h/mL and 393 (391) ng/mL, respectively. In the GAM analysis, ETR AUC or C0 was not significantly associated with reaching viral load <50 copies/mL at Week 48. Older patients and baseline viral load and CD4 cell count, phenotypic sensitivity score (PSS), adherence, baseline fold-change in EC50 (FC to DRV and ETR, age and use of enfuvirtide (ENF) or tenofovir (TDF), were important determinants than pharmacokinetics. Antiviral activity of ETR was observed in patients with PSS<0 irrespective of pharmacokinetics. No apparent relationships were seen between ETR pharmacokinetics and laboratory changes or adverse events, including rash.

**Conclusions**
ETR demonstrated superior activity compared with placebo in the DUET trials at Week 48. Achieving viral load <50 copies/mL at Week 48 in these trials was not influenced by ETR pharmacokinetics, but rather by other drug, disease- and patient-related factors. Furthermore, no relationship between ETR pharmacokinetics and safety was observed.

**Introduction**
ETR is a next-generation NNRTI with potent in vitro activity against both wild-type and NNRTI-resistant HIV.1

**PK/efficacy analysis: GAM**
- Dataset bootstrapped 1,000 times
- Probability of response (viral load <50 copies/mL) was predicted 1,000 times for each subject in the original database using the bootstrapped dataset
- Response rate was predicted for each study arm with and without the additional covariates to each of the individual predictions
- Median error was assessed by comparing a random value between zero and one for each subject, assigning a uniform distribution, and comparing this sampling distribution to the predicted response rate for each model
- If the sampling value was below the predicted probability, the response was considered to have occurred, otherwise the response was considered not to have occurred

**Selection of final GAM**
- No apparent relationship between ETR AUC0–24h and viral load <50 copies/mL at Week 48

**Pharmacokinetics and safety (cont’d)**
- No apparent relationship between ETR AUC0–24h and any of the adverse events

**References**