16th International AIDS Conference

Toronto, Canada - August 13 - 18, 2006

ABSENCE OF TMC114 EXPOSURE-EFFICACY AND EXPOSURE-SAFETY RELATIONSHIPS IN POWER 3

Int Conf AIDS. 2006 Aug 13-18;16 Abstract No. TuPE0078

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BACKGROUND: TMC114 is an HIV protease inhibitor (PI) that is potent against wild-type and PI-resistant HIV strains. The POWER 3 analysis examined the efficacy, safety and pharmacokinetic/pharmacodynamic (PK/PD) relationships of TMC114 coadministered with low-dose ritonavir (TMC114/r) at the recommended dose of 600/100mg bid, in treatment-experienced HIV patients receiving an optimized background regimen (OBR; composed of NRTIs ± enfuvirtide).

METHODS: The TMC114 PK parameters, area under the curve and trough concentration were determined by sparse blood sampling of 292 patients from POWER 3 at Week 24. TMC114 PK/PD relationships were assessed using analysis of covariance models. PD efficacy measures included viral load (VL) change from baseline and proportion of patients with ≥1.0 $\log_{10}$ VL reduction. The inhibitory quotient (IQ), which is the ratio between the steady-state TMC114 trough concentration and baseline TMC114 fold-change in EC_{50}, was also related to the PD efficacy measures. The relationship between TMC114 PK and the occurrence of adverse events of interest as well as TMC114 PK and maximum changes in laboratory parameters were investigated using descriptive methods.

RESULTS: At the recommended TMC114/r dose of 600/100mg bid, TMC114 PK parameters were not significantly associated with virologic response at Week 24. The IQ was the strongest predictor of virologic response (p value <0.001), with the relationship driven by baseline TMC114 fold change in EC_{50}; other predictors were baseline VL and the number of sensitive antiretrovirals in the OBR. No clinically relevant exposure-safety relationships were observed.

CONCLUSIONS: In the absence of exposure-efficacy and exposure-toxicity relationships at the recommended TMC114/r dose, therapeutic drug monitoring for TMC114 is unlikely to play a role in the management of HIV infection.

2006-08-13
TuPE0078
