A-962

Pharmacokinetic (PK) Evaluation of Darunavir/Ritonavir (DRV/r) and Raltegravir (RAL) in Healthy Subjects

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Background: Both DRV/r, a next generation PI, and RAL are currently used in the clinical setting. DRV/r is a protease inhibitor (PI) that is co-administered with a low dose of ritonavir (200 mg). The effect of DRV/r on RAL pharmacokinetics has not been evaluated in a controlled clinical setting. Preclinical studies have shown a modest effect on the pharmacokinetics of other PIs, such as tipranavir (RTV) co-administered with DRV/r. This study evaluated the effect of DRV/r co-administration on the PK of RAL.

Methods: Eighteen healthy subjects were enrolled in an open-label, sequential 2-period study. In Period 1, all subjects were administered 400 mg RAL q12hr for 4 days. In Period 2, subjects were administered 400 mg DRV and 100 mg RAL q12hr for 12 days. Period 2 immediately followed Period 1. Doses were administered with a meal.

Results: Eight subjects presented with a clinical adverse experience (AE) of rash. Seven were rated mild to moderate by intensity, one was rated as serious AE of rash. No severe AEs were reported. There were no deaths or serious AEs. No serious drug-related AEs were reported. Two subjects reported an AE of rash that was considered to be drug-related. These AEs were reported for 1 subject on Day 1 and 1 subject on Day 10 of Period 2.

Conclusions: Co-administration of DRV/r and RAL resulted in a modest effect on the PK of RAL, with no clinically important changes in DRV/r pharmacokinetics.

Introduction

• Raltegravir (RAL) is a novel HIV-1 integrase inhibitor with potent in vitro and clinical activity against HIV-1.
• DRV/r is highly effective in the treatment and suppression of HIV-1 infection.

Analytical and Pharmacokinetic Methods

• Plasma samples were analyzed for RAL concentrations using a validated HPLC – MS/MS assay.
• Plasma samples were analyzed for DRV and RTV concentrations using a validated HPLC – MSD/MS assay.
• Cmax and Tmax were determined by inspection.

Statistical Analysis

• Confidence intervals for RAL and DRV Cmax, AUC0-12hr, and Cmax were constructed using the appropriate mixed-effects linear model.