

**Abstract: 28**

*Drug Interactions*

**Relative bioavailability and pharmacokinetics of Darunavir when boosted with the pharmacoenhancer GS-9350 versus ritonavir**

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**Introduction:** GS-9350 is a specific, potent, mechanism-based inhibitor of human cytochrome P450 3A (CYP3A) and has demonstrated to effectively boost exposure of orally administered CYP3A substrates, including midazolam, elvitegravir and atazanavir *in vivo*. Ritonavir- boosted darunavir [DRV; 800 with 100 mg of ritonavir (r)] is a DHHS-preferred HIV protease inhibitor for use in treatment naïve HIV patients. This study evaluated the pharmacokinetics (PK) of DRV/GS-9350 compared to DRV/r.

**Methods:** This was a randomized, 24-day, two-period (each of 10 days), multiple dose, two-sequence, crossover study in healthy volunteers (n=17/sequence). Subjects received Treatment A, DRV/GS-9350 (800/150 mg QD) or Treatment B, DRV/r (800/100 mg QD) under fed conditions, with a 4-day washout between treatments. DRV, GS-9350, and ritonavir PK were assessed on Day 10 of each period. Predefined lack of PK alteration bounds for 90% confidence intervals (CI) about the geometric mean ratio (GMR) were 80-125% for DRV  $C_{max}$ ,  $C_{tau}$ , and  $AUC_{tau}$ .

**Results:** Thirty-three subjects enrolled and thirty-one completed the study; one subject discontinued due to a treatment-related adverse event (maculopapular rash, Treatment A); the other was discontinued at the investigator's discretion. For the PK analyses set (n=31), the GMR(%) (90% CI) for  $AUC_{tau}$  [102 (97.4, 106)] and  $C_{max}$  [103 (100, 106)] were within limits of bioequivalence following once-daily dosing of DRV/GS-9350 versus DRV/r.  $C_{tau}$  values were lower [GMR (90% CI): 69.4 (59.0, 81.7)], secondary to unexpected increasing DRV concentrations at the 24-hr time point for the DRV/r treatment. DRV predose concentrations ( $C_{0h}$ ) following observed, multiple doses of study drug at steady-state were also equivalent [GMR (90% CI): 89.4 (80.4, 99.4)] between both treatments and > 37-fold above the protein-adjusted  $EC_{50}$  for wild-type virus (55 ng/mL).

**Conclusion:** GS-9350 adequately boosts DRV, resulting in equivalent  $C_{max}$  and  $AUC_{tau}$  and with trough concentrations established to have effective and durable antiviral response in treatment-naïve patients.

*Conflict of interest*

*financial relationship(s): All authors are employees of the respective pharmaceutical companies*