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O413 Pharmacokinetics (PK) of once-daily etravirine (ETR) without and with once-daily darunavir/ritonavir (DRV/r) in antiretroviral-naïve HIV-1 infected adults

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Purpose of the study

ETR is potent against wild-type HIV (protein-binding adjusted EC_{50} of 4 ng/mL), has a terminal elimination half-life of 30–40 hours, and is a candidate for once-daily (QD) dosing. In healthy volunteers, ETR AUC was similar, C_{max} was 44% higher and C_{min} was 25% lower for QD vs. twice-daily dosing (*Ann Pharmacother* 2008; 42: 757-65). Once-daily DRV/r was shown to be effective and well-tolerated in antiretroviral (ARV)-naïve patients (*AIDS* 2008; 22: 1389-97). This multicenter, open-label Phase IIa trial evaluates PK and short-term safety and efficacy of ETR 400 mg QD plus TDF/FTC 300/200 mg QD without and then with DRV/r 800/100 mg QD.

Methods

ARV-naïve adults with HIV-1, no evidence of resistance to study drugs, and without HBV/HCV co-infection were eligible. Subjects received ETR 400 mg QD with TDF/FTC 300/200 mg QD for 14 days, then added DRV/r 800/100 mg QD on days 15–28. ETR was discontinued days 29–42. Intensive PK sampling was performed over 24 hours on day 14 for ETR, and day 28 for ETR, DRV and ritonavir (RTV). All doses were administered following a meal. PK parameters were determined using a non-compartmental model with extravascular input and evaluated by least squares mean (LSM) ratios with 90% confidence intervals (CI).

Summary of results

Twenty-three subjects (20 men) enrolled: nine Black, nine Caucasian and five Hispanic with mean age 35.9 years; mean baseline (BL) viral load (VL) 4.2$\log_{10}$ copies/mL; median BL CD4 402 cells/mm^3. DRV PK was slightly higher and RTV PK slightly lower when compared to historic control (ARTEMIS week 4 PK study). Mean VL decline was 1.7 $\log_{10}$ copies/mL at day 14 (n = 21) and 2.0 $\log_{10}$ copies/mL at day 42 (n = 20). Median CD4 increase was 56 cells/mm^3 (day 42). Most common treatment-emergent AEs were nausea (n = 4), headache (n = 3), rash (n = 3), and flatulence (n = 2). No serious or grade 3/4 AEs were reported; no AEs led to discontinuation. The impact on metabolic parameters was small when ETR was given with or without DRV/r. (Table 1).

Conclusion

Addition of DRV/r QD to ETR QD had no significant impact on ETR PK and exposure to ETR was adequate with and without DRV/r. PK data and short-term safety and efficacy support further clinical investigation of ETR 400 mg QD in HIV-1 infected patients.

Table 1:

Parameter, mean (SD)	**Day 14 ETR+TDF/FTC n = 21**		**Day 28 ETR+TDF/FTC+DRV/r n = 20***	
	ETR	ETR	DRV	Ritonavir
C_{max}, ng/mL	790 (287)	801 (327)	7008 (1514)	465 (231)
C_{min}, ng/mL	233 (130)	236 (168)	1049 (616)	27 (21)
$AUC_{24\ h}$, ng•h/mL	10410 (4186)	10720 (5459)	76130 (22080)	4128 (1854)

*n = 19 for $AUC_{24\ h}$