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Pharmacokinetic interaction between etravirine and lopinavir/ritonavir

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Abstract

Background

Etravirine (ETR; TMC125) is a next-generation NNRTI with demonstrated activity in treatment-experienced, HIV-1-infected patients. A previous interaction trial in HIV-negative volunteers demonstrated increased ETR exposure when co-administered with LPV/r (soft-gel formulation). This study re-evaluated the pharmacokinetics of ETR and LPV/r when LPV/r was administered as the Meltrex® formulation.

Methods

Open-label, randomized, two-way, two-period crossover trial. ETR 200mg bid was given for 8 days. After 14 days washout, LPV/r 400/100mg bid was administered for 16 days; ETR 200mg bid was co-administered on Days 9–16. Steady-state pharmacokinetics were assessed over 12 hours for ETR, lopinavir (LPV) and ritonavir (RTV) alone and when co-administered. Pharmacokinetic (PK) parameters were obtained by non-compartmental analysis. Safety and tolerability were assessed.

Results

Sixteen volunteers participated (11 male/five female). PK results are given below (Table 1).

Table 1. Mean (± SD) PK parameters for ETR and LPV alone and co-administered

ETR	Alone (N=16)	With LPV/r (N=16)	LSM ratio (90% CI)
C_{min} (ng/mL)	451 ± 121	253 ± 84	0.55 (0.49–0.62)
C_{max} (ng/mL)	905 ± 187	643 ± 163	0.70 (0.64–0.78)
AUC_{12h} (ng•h/mL)	8,036 ± 1,779	5,250 ± 1,416	0.65 (0.59–0.71)
LPV	**Alone (N=16)**	**With ETR (N=16)**	**LSM ratio (90% CI)**
C_{min} (µg/mL)	5.3 ± 1.9	4.3 ± 1.5	0.80 (0.73–0.88)
C_{max} (µg/mL)	11.2 ± 2.9	9.8 ± 1.9	0.89 (0.82–0.96)
AUC_{12h} (µg•h/mL)	96.8 ± 21.8	84.5 ± 17.7	0.87 (0.83–0.92)

SD = standard deviation; LSM = least square means; CI = confidence interval; C_{min} = minimum plasma concentration; C_{max} = maximum plasma concentration; AUC_{12h} = area under the plasma concentration-time curve from time of administration to 12 hours after dosing

RTV pharmacokinetics were unchanged. The most frequent adverse event (AE) was headache in six volunteers (grade 1). One grade 3 increase of triglycerides was reported during co-administration.

Conclusions

In contrast to the results of the study performed with the soft-gel LPV/r, co-administration of ETR with LPV/r (Meltrex®) resulted in a 30–45% decrease in ETR pharmacokinetics. The decrease of LPV PK parameters by 13–20% when combined with ETR is similar to earlier reported data and is not considered clinically relevant. Given that the effect of LPV/r on ETR pharmacokinetics is comparable to the effect of darunavir/ritonavir (DRV/r) on ETR pharmacokinetics shown in previous trials, which demonstrated favorable ETR efficacy and safety, ETR and LPV/r can be co-administered without dose adjustments.

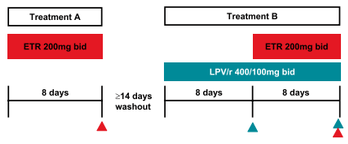
Introduction

- ETR is a next-generation NNRTI with potent activity against both wild-type HIV-1 and HIV-1 resistant to first-generation NNRTIs[1]
- Two Phase III trials (DUET-1 and DUET-2) demonstrated significant antiviral benefit over 96 weeks of treatment with ETR in treatment-experienced patients with resistance to first-generation NNRTIs. Except for a higher incidence of rash, patients treated with ETR had an AE profile similar to placebo[2–4]
- ETR is predominantly metabolized by the cytochrome P450 (CYP) enzymes 3A, 2C9 and 2C19, followed by glucuronidation; it is an inducer of CYP3A4 and an inhibitor of CYP2C9, CYP2C19 and P-glycoprotein
- The protease inhibitor LPV/r is indicated for the treatment of HIV-1 infection
- LPV/r is an inducer of CYP1A2, CYP2C9, CYP2C19 and an inhibitor of CYP3A[5]
- A previous interaction trial in HIV-negative volunteers demonstrated increased ETR exposure when an earlier formulation of ETR was co-administered with the soft-gel formulation of LPV/r[6]
- This trial re-evaluated the PK interaction between ETR and LPV/r using the current formulation for both drugs (i.e. ETR spray-dried formulation and LPV/r produced by melt extrusion technology)

Study design

- TMC125-C197 was a Phase I, open-label, two-way, two-period, randomized crossover trial in 16 HIV-negative volunteers
- Two treatment sessions (A and B) were scheduled for all volunteers, separated by a washout period of at least 14 days, as shown in the study design scheme. Half of the volunteers were randomized to start with Treatment A and half were randomized to start with Treatment B
- ETR was administered as 200mg bid; all doses were taken within 10 minutes after breakfast and dinner
- LPV/r was administered as 400/100mg bid of the Meltrex® formulation, within 10 minutes after breakfast and dinner
- Post-treatment safety visits took place 7 and 31 (±1) days after the last intake of trial medication
- The trial protocol was reviewed and approved by the appropriate institutional ethics committee and health authorities; the trial was conducted in accordance with the Declaration of Helsinki

Study design (cont'd)



▲ 12-hour PK analysis of ETR on Day 8 of Treatment A and Day 16 of Treatment B
▲ 12-hour PK analysis of LPV and RTV, determined on Day 8 and Day 16 of Treatment B

Safety and tolerability assessments were performed throughout the trial until at least 30 days after the last trial medication intake

PK analyses

- Plasma concentrations of ETR were determined using a validated LC-MS/MS method (LLOQ 2ng/mL)
- Plasma concentrations of LPV and RTV were determined using a validated LC-MS/MS method (LLOQ 10ng/mL and 5ng/mL, respectively)
- A non-compartmental model with extravascular input was used for the PK analysis
- PK and statistical PK analyses were performed using WinNonlin Professional™ (version 4.1, Pharsight Corporation, Mountain View, California, USA) and SAS System for Windows® version 9.1.3 (SAS Institute Inc., Cary NC 27512–8000, USA)

LC-MS/MS = liquid chromatography-tandem mass spectrometry
LLOQ = lower limit of quantification

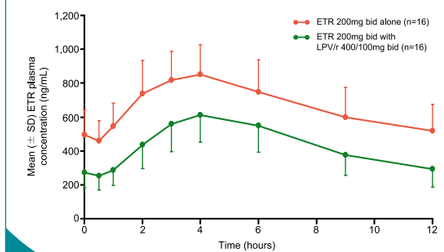
PK and safety parameters and statistical analyses

- Primary PK parameters
  - C_{min} (ng/mL)
  - C_{max} (ng/mL)
  - AUC_{12h} (ng•h/mL)
- Safety parameters
  - AEs, laboratory assessments, electrocardiogram, vital signs assessment and physical examinations were evaluated throughout the study
  - severity and drug relationship of AEs to ETR, LPV and/or RTV were recorded
- Statistical analyses
  - descriptive statistics were calculated for the PK parameters of ETR, LPV and RTV
  - LSM ratios and 90% CIs were estimated with a linear mixed-effects model
  - safety parameters were evaluated by descriptive statistics and frequency tabulations

Demographics

Demographic parameter	All volunteers (N=16)
Age, years, median (range)	45 (20–53)
Height, cm, median (range)	175 (158–193)
Weight, kg, median (range)	70 (53–94)
Body mass index, kg/m², median (range)	23 (19–29)
Gender, n (%)	
Male	11 (69)
Female	5 (31)
Ethnic origin, n (%)	
Caucasian	16 (100)

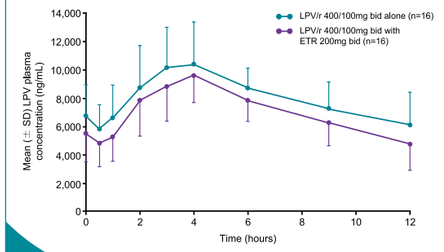
ETR plasma PK profile



ETR PK parameters

PK parameter	ETR alone (Reference) (mean ± SD) (n=16)	ETR + LPV/r (Test) (mean ± SD) (n=16)	LSM ratio (Test/Reference) (90% CI)
C_{min} (ng/mL)	451 ± 121	253 ± 84	0.55 (0.49–0.62)
C_{max} (ng/mL)	905 ± 187	643 ± 163	0.70 (0.64–0.78)
AUC_{12h} (ng•h/mL)	8,036 ± 1,779	5,250 ± 1,416	0.65 (0.59–0.71)

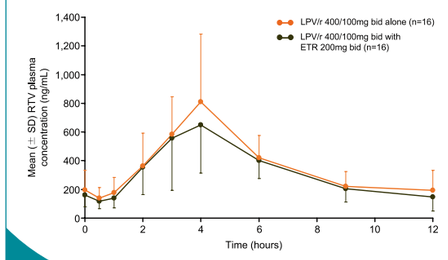
LPV plasma PK profile



LPV PK parameters

PK parameter	LPV alone (Reference) (mean ± SD) (n=16)	LPV + ETR (Test) (mean ± SD) (n=16)	LSM ratio (Test/Reference) (90% CI)
C_{min} (ng/mL)	5,333 ± 1,850	4,322 ± 1,527	0.80 (0.73–0.88)
C_{max} (ng/mL)	11,170 ± 2,909	9,792 ± 1,906	0.89 (0.82–0.96)
AUC_{12h} (ng•h/mL)	96,790 ± 21,790	84,520 ± 17,710	0.87 (0.83–0.92)

RTV plasma PK profile



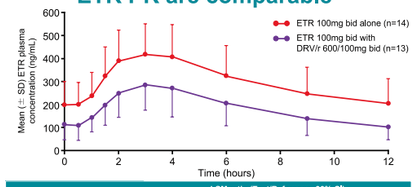
RTV PK parameters

PK parameter	RTV alone (Reference) (mean ± SD) (n=16)	RTV + ETR (Test) (mean ± SD) (n=16)	LSM ratio (Test/Reference) (90% CI)
C_{min} (ng/mL)	125 ± 72	107 ± 53	0.86 (0.76–0.97)
C_{max} (ng/mL)	845 ± 452	668 ± 341	0.81 (0.69–0.95)
AUC_{12h} (ng•h/mL)	4,415 ± 1,792	3,925 ± 1,472	0.89 (0.81–0.98)

Safety summary

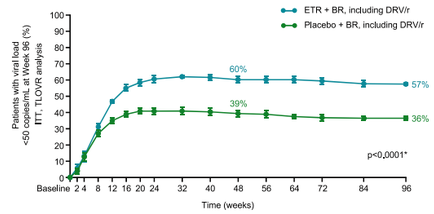
- No serious AEs were reported
- None of the volunteers discontinued the trial
- The most frequently reported AE was headache (six volunteers)
- All AEs reported during the treatment periods were mild (grade 1) or moderate (grade 2) in severity except for a grade 3 increase of triglycerides during co-administration of ETR and LPV/r; two other grade 3 laboratory abnormalities were observed during the co-administration phase (increase of total cholesterol and low-density lipoprotein)
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or physical examinations

Effects of LPV/r and DRV/r on ETR PK are comparable[7]



PK parameter	LSM ratio (Test/Reference, 90% CI) DRV/r	LPV/r
C_{min} (ng/mL)	0.51 (0.44–0.61)	0.55 (0.49–0.62)
C_{max} (ng/mL)	0.68 (0.57–0.82)	0.70 (0.64–0.78)
AUC_{12h} (ng•h/mL)	0.63 (0.54–0.73)	0.65 (0.59–0.71)

Efficacy of ETR co-administered with DRV/r at Week 96[4]



*Logistic regression model controlling for baseline viral load, enfuvirtide use and study number; ITT = intent-to-treat; TLOVR = time-to-loss of virologic response imputation algorithm; BR = background regimen

Conclusions

- ETR had no clinically relevant effect on the pharmacokinetics of LPV and RTV
- When co-administered with the Meltrex® formulation of LPV/r, ETR PK parameters decreased by 30–45%
- The effect of the Meltrex® formulation of LPV/r on ETR is comparable to that seen with DRV/r[7]
  - efficacy and safety of ETR in the presence of DRV/r was demonstrated in DUET-1 and DUET-2[4]
- Co-administration of ETR and LPV/r was generally safe and well tolerated
- ETR can be co-administered with LPV/r without dose adjustments

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